

sional house officers serve in order to prepare for a career in pathology. Others spend a period of their clinical internship in the laboratory. Others visit the laboratory freely. Still others enter the laboratory to secure enlightenment on materials from their patients. Occasionally interns confer with the pathologists to discuss the diagnosis and treatment of their patients, or to consult in regard to scientific problems. All these circumstances offer the pathologists an opportunity to make his imprint on the "budding talent." He should know the house staff and what the objectives of each member are. In spite of insistence on the conception of the hospital period as educational in the sense of the graduate school, its vocational aspects cannot be overlooked.

The house officer in pathology, looking forward to a career in that subject, is all too ready to concentrate on methods and materials. As a balance against this tendency he should be encouraged to find a place in nature for the phenomena he observes and also to consider their bearing on disease in the living. The house officer working in pathology as a preparation for or as a part of his clinical internship has no need of encouragement to look for its clinical application. In his case the urge to make all the factors 'practical' may lead him to lose sight of his primary objective, namely, the study of the nature of disease. The value to be obtained from periods of different length spent in the laboratory cannot be calculated mathematically, but the worth progresses more nearly in geometrical than in arithmetical proportion. If a man can give two years to such work, his second year is more than twice as valuable as his first year. If he gives only one year, his second half-year has more than twice the value of his first half year. Four months is the minimum amount of time that can be spent usefully in the laboratory. After a year's service the intern may subsequently make genuine progress in the pathology of a special field as an adjunct to his clinical work, but two years give him a more satisfactory background. From four to six months is in most instances inadequate for this purpose, but time so spent still may have distinct educational worth.

The house officers who visit the laboratory for examination of materials from their patients and explanation of reports, or to consult in regard to other matters, are not subjected to a continuous and concentrated influence by the pathologist. The manner of reception by the pathologist and his interest in the material or the problem, quite as much as the inherent interest of the house officer, determine the frequency of these visits and accordingly such benefits as the pathologist may confer. The educational importance when properly nurtured, can be far-reaching, for even in a few minutes the stimulus to further study and to appreciation of general implications can be suggested.

If imbued with the spirit of scientific curiosity, the pathologist may, in addition to imparting the results of immediate observation, instill a like curiosity in the house officers of all classes. Case reports of especial interest can be placed in the literature, for their own sake and for the collection of data when a sufficient number justifies organized and statistical examination. Material on a given condition may accumulate in the laboratory in adequate amounts for investigative compilation. The place of the intern in these investigations depends on his desire to enlarge the sum of human knowledge, his ability to make exact observations and occasionally on his constructive imagination. His qualifications to take part in research other than initiative and industry, rest on his capacity to make and record the observations required. His routine as an intern generally precludes the learning of intricate technical methods, nor can his research depend on great experience. In encouraging him to investigation his senior must adapt the problem to the house officer's limitations and not impose difficulties of technique that will serve either as a diversion from the objective of a general training or as a source of discouragement. If time and training permit only the preparation of case reports, energy is not wasted for these have a general value and accustom the house officer to the library and its stores, thus preparing him to consult original sources when he is no longer sheltered in the fold of the hospital.

The Pathologist's Opportunities in Medical Research

DR C. C. BASS, New Orleans. The profound influence of pathology on the progress of medicine and the development of our knowledge of disease since the earliest days indicates the abundance of opportunities in medical research which the pathologist may enjoy today. Many of us, no doubt, fail to realize the extent to which the accomplishments of the great men in medicine have rested either directly or indirectly, on pathology. Medical bacteriology is that branch of pathology which deals with infective diseases and their causation. While general bacteriology has developed as a separate branch of science, medical bacteriology has developed largely as a part of the broad subject of pathology or in close relation and association with it. With the discovery of bacteria as the chief specific cause of most diseases and as a result of researches into the influences that favor, limit or resist their invasion immunology and serology have developed, also within the general field of pathology. Through these branches which have been so inviting for research, exact means of diagnosis and specific methods of treatment have been discovered whose value and influence on medicine and surgery it is almost impossible to estimate.

The greatly increased interest in pathology during the past fifty or sixty years and the exact methods of studying diseases in the light of bacteriology have led to the discovery of protozoa and other parasites as the cause of many diseases and to the development of another branch of science, parasitology. As in the case of bacteriology, general parasitology has developed as a separate branch of science, but medical parasitology has developed in close relation with pathology, again greatly increasing the pathologist's opportunities for research. And pathologists have contributed largely to the discoveries and advances relative to the nature and cause of these important diseases. Has the field been exhausted by the past great and productive activity, or are there still opportunities left? My answer is that there has never been a time when the pathologist's opportunities for research were greater, or gave greater promise of success, than today. The young man who has research ability can find unlimited opportunities in the field of pathology.

The Pathologist in a Private Clinical Laboratory

DR KENNETH M. LYNCH, Charleston, S. C. Because hospital and medical school pathologists have been mainly concerned with the study and teaching of general pathology, morbid anatomy, autopsy technic and tissue diagnosis, there came to be a distinction between pathologists and clinical pathologists, the latter having little to do with this work, except in the case of a hospital connection, but rather being mainly concerned with medical bacteriology, parasitology, serology and chemistry. Even in some hospitals and private laboratories the services of pathologist and clinical pathologist are separate, and, although some hospital pathologists may have charge of the clinical laboratory work and while some privately practicing pathologists may have hospital connections through which they may do postmortems and tissue diagnosis the clinical pathologist doing only private laboratory work usually has little opportunity in this field and commonly does not undertake it or claim proficiency in it. At least he should not unless his training qualifies him for it and unless his practice of it is sufficient to enable him to retain his proficiency.

In response to the demand on the part of practitioners for laboratory service for patients not in hospitals and in hospitals not having such organized service, many clinical pathologists have set up private laboratories and entered into the practice of the specialty. Some of these have hospital laboratory connections some have not. In such private practice of laboratory medicine and in the practice of pathology as a whole, the specialist is naturally completely subservient to the profession. His clientele is composed not of patients but of the physicians of patients. Other specialists doing even referred work in large part usually deal directly with the patient and are responsible more or less directly to him and so retain control of their own work. If the laboratory technician does not do those parts of the work which require a medical training, if he simply examines substances delivered to him and reports on

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WITH SIXTEEN PLATES AND SIXTY FIVE
FIGURES IN THE TEXT



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1944

ASSOCIATION NEWS

be no question of cost there, but because of the administrative difficulties of the organization, it is utterly impossible to increase one's force sufficiently to carry on the work.

DR. WALTER FREEMAN, Washington D. C. Dr. Prince has painted a rather gloomy picture of the outlook in the Veterans' Bureau, and I might say that it applies to the government services as well. However, I think there is a side to the picture that ought not to be left out. In the first place, a man going into the Veterans' Bureau, through civil service, I think, is started at a salary of \$3200. He has to have his internship. He is then given whatever training he will get at the hands of Dr. Prince or his colleagues. I think we will admit that four months is a rather inadequate time for such training in general laboratory work, particularly if it includes roentgenology. However, for the man who has put in a year after his internship in pathology in one of the well recognized medical centers or pathologic institutes, it would seem to me that this would afford an unrivaled opportunity both for self-preservation and for the study of pathology. The army needs pathologists and it is willing to pay them. The great difficulty is in getting a start. Once the men get a start in the government services they go along swimmingly. But they cannot be taken in as pathologists when they are mere apprentices. What Dr. Wilson has outlined as the necessary training for pathologists evidently depends on the man himself. Some can get in a year what other men would probably need five years to get. I would suggest, however, the necessity of a man being untrammelled in his first year of postgraduate study. It is then that his enthusiasm is at the highest pitch and only at that time will he be willing to work fourteen, sixteen or eighteen hours a day. He should be given this outlook, then, of service in the armed forces of the United States or elsewhere or in some other position and told to go to it for a year or two and then to get his experience and further training in the Veterans Bureau or some other location. With such a plan I think in a few years there would be no cry for more pathologists.

DR. E. STANLEY RYERSON, Toronto. It seems to me that there is one aspect of the relation and the importance of pathology to medicine that has not perhaps been given the fullest amount of consideration. We have been hearing of the study of disease from the standpoint of the autopsy of pathologic anatomy and of bacteriology but it should not be forgotten that in the past ten years considerable advances have been made in pathologic chemistry. In the opportunities for research and development in pathology, that aspect of pathology should not be overlooked.

DR. ALFRED PLAUT, New York. It may not have struck some here that we have heard the word pathology frequently and the words pathologic anatomy seldom. When I came to this country from Germany several years ago I considered myself a pathologist, without thinking much of what this term meant. I realized soon that the pathologist in the United States is quite different from the pathologist in middle Europe. In Germany, especially pathology is entirely different. I have always considered the urinalysis and the blood count as belonging to the realm of the medical man. On coming here I realized that it belonged to my realm as a pathologist. Is not the science of the chemical and physiochemical consistency of freshly voided urine something belonging more to the medical man especially the one who is chemically trained? The hematologist is a medical man and not a pathologist. Is it right, is it fair, to the pathologist to burden him with the so-called routine work of the urinalysis and blood count? Is it really for the benefit of hematology and of urinalysis to be taken away from medical men and given over to the pathologist? Have not the greatest advances in chemical studies of urine for instance, been made by medical men and is not the same true in the advances of hematology? Furthermore, those who are now of the opinion that there is an enormous waste of time, money, energy and material in superfluous so-called routine analyses and blood counts will find that as soon as the urinalyses and blood counts are given to the medical men as soon as there is again a personal connection between the man who treats the patient and the man who does the blood count, especially when he does it himself this waste will be abolished.

DR. W. J. GAMBLE, Bay City, Mich. Some time ago I sent out a questionnaire to find out how many people were practicing pathology in this country. It was surprising to learn that there are less than 500 persons practicing the so-called specialty of pathology or clinical pathologists and others doing research work. That leaves available for more than 8000 hospitals less than 500 men. It therefore becomes necessary for individuals whether they like to do clinical pathology or not, to cover this so-called hybrid specialty of clinical pathology. I think that would answer the question. Some one has to do the work. One of the university chiefs said that when the so-called pathologists or clinical pathologists are sufficiently paid, there will be no lack of men.

DR. LOUIS B. WILSON, Rochester, Minn. I should like to mention an impression which I have obtained in going about and talking with pathologists and from the letters of pathologists in reply to the questionnaire sent out by the Council, namely that there are many pathologists in responsible positions in large hospitals and with important university connections who frankly are not interested in autopsy work and say so. They are interested in teaching and they are interested in research but they are not interested in practicing pathology. They have a conception of pathology as one of the fundamental branches like anatomy or physiology, in which a man's interest must be in study or in teaching. But pathology has a practical side as well. It does not seem to me that a man can preserve his highest function his balance his judgment so as to teach pathology in the proper manner to students if he does not practice pathology any more than a surgeon who merely studied and talked surgery could preserve his breadth of view of surgical practices. It is perfectly all right to have men whose major interests in pathology are in research and men whose major interests in pathology are in teaching but if they are to preserve their balance and if our departments of pathology are to be balanced departments in university work it seems to me that the pathologist must practice pathology. Certain pathologists are so imbued with the sense of teaching that their only conception of a graduate student is a chap who is willing to sit down in a row with others and be talked to have facts poured into him. That is not the attitude of student I come in contact with. That is not the attitude of the best men from the medical schools today who are seeking opportunities to perfect themselves further in technique and in judgment in the practice of pathology. The term graduate student has unfortunately come to mean, in this country, the man who is willing to give three whole weeks to the study of some specialty. I wish that we could forget it. I am absolutely convinced that many of the men directing the destinies of pathology in our medical schools today have an improper conception of the desire of some of the best men being graduated from our schools for opportunity to work under good guidance in their departments.

(To be continued)

MEDICAL BROADCAST FOR THE WEEK

American Medical Association Health Talks

The American Medical Association broadcasts daily at 10 o'clock, Central Standard Time with the exception of Tuesday when the health message is delivered at 10:30 and Friday at 9:45 over Station WBBM (770 kilocycles or 389.4 meters).

The program for the week of April 7-12 is as follows:

- April 7 Smallpox
- April 8 Care of the School Child's Health
- April 9 Preventing Crime
- April 10 Eyes for School
- April 11 Gas Poisoning
- April 12 The Medicine of the Sun

Five Minute Health Talks may be heard over the Columbia Broadcasting System daily from 12 noon to 12:05 p.m.

The program for the week is as follows:

- April 7 History Measures the Medical Milestones
- April 8 It's Only Chickenpox
- April 9 Pet Ideas About Colds
- April 10 Marathonitis
- April 11 Vagaries of the Vegetarians
- April 12 The National Narcotic Nuisance

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NUMBER 14

Johnson D O, Louisville, Dr J Watts Stovall Grayson, Dr Frank L. Johnson, Livermore Mr Addison Dimmitt, Louisville Dr Lawrence T Minish, Frankfort, and Dr Arthur T McCormack, Louisville, secretary

LOUISIANA

Society News—The New Orleans Gastro-Enterological Society, January 23, elected Dr Daniel N Silverman president for the ensuing year—Dr Henry W E Walther, New Orleans, addressed the St. Tammany Parish Medical Society Mandeville February 14, on Urologic Problems in General Practice and Suggestions for Their Solution

Munch Ordered to Prison—The fifth circuit federal court of appeals at New Orleans March 22, ordered the immediate issuance of a mandate for the incarceration of George A Munch Tampa Fla convicted of mail fraud in connection with alleged 'diploma mill' operation The court order was issued following the second confirmation of Munch's conviction

MARYLAND

Society News—A survey of the mental hygiene activities of Boston, with Dr George H Preston commissioner of mental hygiene of Maryland as director has been undertaken by city and state agencies Dr Preston will devote part time to the task, with the assistance of a full-time psychiatric social worker The survey is expected to be completed in October

Dr Kelly Presents Books to Welch Library—A collection of 500 books relating to the advancement of women in all fields was presented March 14 to the Welch Medical Library of Johns Hopkins University by Dr Howard A Kelly, emeritus professor of gynecology It will be known as the Florence Nightingale Library The collection includes volumes relating to Miss Nightingale, books pertaining to the political and social advancement of women since 1793 and many rare editions Dr Stephen d Irsay, associate in the Institute of the History of Medicine, Johns Hopkins University will sail for Europe in a few weeks to assemble data on the history of universities for the Welch Library Books old registers biographies of eminent professors and correspondence will be gathered While in Paris Dr d Irsay will address the Carnegie Endowment for World Peace on 'The International Character of Universities as Developed by Their Histories'

Dr Welch Honored—Dr William Henry Welch, professor of the history of medicine, Johns Hopkins University School of Medicine, will be honored on his eightieth birthday, April 8 by a celebration, which will take place simultaneously in London Paris, Berlin, Leipzig Tokyo and Peiping, Baltimore Cincinnati, New Haven, New York and Washington D C President Hoover will speak in Memorial Continental Hall Washington, at noon, and will be heard over a national hookup of the National Broadcasting Company One feature of the celebration will be the presentation of the first print of the dry point portrait made by Alfred Huttv, the etcher, Charleston, S C, and the simultaneous presentation of other prints from the same etching to more than forty institutions in this country and abroad Dr Simon Flexner, New York is chairman of the executive committee in charge of arrangements Dr Livingston Farrand, Ithaca N Y, will deliver the opening address at the Washington ceremonies

MASSACHUSETTS

Bill Introduced—House bill 1196 proposes to create a commission to investigate the prevalence of addiction to habit-forming drugs

MISSISSIPPI

Bill Enacted—S B 13 safeguarding the distribution and sale of certain dangerous caustic or corrosive acids alkalis and other poisonous substances by requiring that they be labeled 'Poison,' has become a law

Bills Introduced—H B 567 proposes to levy on physicians an occupational tax equal to 0.25 per cent of gross income H B 242 proposes to regulate the practice of podiatry and to provide for the examination and licensing of podiatrists by the state board of health

MISSOURI

Court Upholds Revocation of Dr Ball's License—The Missouri Supreme Court March 4 upheld the action of the state board of health in revoking the license of Dr Samuel E Ball, Excelsior Springs for circuitously and illegally soliciting business for his sanatorium through the Health Culture company which he owned The license was revoked in November, 1926

Physicians Tried for Narcotic Violations—Dr George W Benitz St Joseph was sentenced in federal court to one year and three months in the penitentiary at Leavenworth and fined \$1,000 for violation of the Harrison Narcotic Law at St Joseph March 3 Dr Fenton N Goodson, colored St Joseph, pleaded guilty to the same offense and is serving his sentence at Leavenworth Dr Collis I Roundy St Joseph will soon be tried, it is said, having been charged with the same offense

Dr Graham to Lecture in Australia—Dr Evarts R Graham, St. Louis professor of surgery, Washington University School of Medicine will leave for Australia in June to give a series of six lectures at the University of Melbourne during the last two weeks of July on chest surgery and conditions of the gallbladder Dr Graham and his family will return in September Dr Graham did pioneer work in the development of cholecystography

Society News—Dr Hyman I Spector gave a lantern slide demonstration of 'Study of Lung Abscesses with Special Emphasis on Conservative Treatment' before the St. Louis Medical Society March 25 Dr Jacob J Singer spoke on 'Tumors of the Chest' and Dr Leroy Sante 'Use of X-Rays in the Detection of Chronic Lung Suppuration'—The Clay County Medical Society was addressed, recently at Excelsior Springs by Dr Samuel D Henry on 'Acute Infections in the Adult Respiratory Tract' and by Dr Burton Valtby Liberty on 'Acute Infections of the Respiratory Tract in Children'—Dr Paul F Cole Springfield gave a paper on 'A Tour of the Colon with an X-Ray Machine' before a recent meeting of the Greene County Medical Society—The March 4 meeting of the Jasper County Medical Society was addressed at Joplin by Dr Edward J Burch, Carthage on 'Management of Normal Labor'—The St. Louis County Medical Society was addressed at Kirkwood March 13 by Dr Theodore C Hempelmann, St. Louis on 'Throat Infections in Children'—Drs Alphonse McMahon and William T Coughlin, St. Louis addressed the Central Illinois Medical Association, March 25 at Decatur, Ill on 'The Heart in Hyperthyroidism' and 'Early Diagnosis and Treatment of Tumors of the Brain,' respectively

NEBRASKA

Graduate Course Offered at State University—The University of Nebraska College of Medicine will offer a graduate course May 5-12, preceding the annual meeting of the state medical society at Lincoln May 13-15 This year the course will be offered under the auspices of the department of internal medicine and will be confined largely to practical work in the wards and clinics The major interest will center around diseases of the lungs as tuberculosis the pneumonias pneumococcal infections, asthma, bronchiectasis, and post-operative pulmonary conditions, diseases of metabolism majoring in thyroid diseases and diabetes, diseases of the circulatory system and blood-forming organs, diseases of the gastrointestinal tract, manifestations of anaphylaxis, the arthritides and diseases of the skin The library will be available at all times Work will begin at 8 o'clock each morning The fee for this course will be \$10 and the number accepted will be limited to thirty Unless ten have registered by April 15 the course will be withdrawn Address communications to the dean's office

NEW YORK

Society News—The Medical Society of the County of Albany was addressed at Albany, March 26 by Dr Richard Kovacs New York, on 'The Present Status of Physical Therapy,' and by Dr Edward S Godfrey Jr Rationale of the New Communicable Disease Regulations'

Personal—Dr Charles I Maggio resigned his position as a medical examiner in the state department of labor Rochester Bureau of Workmen's Compensation effective March 15, to enter private practice Dr Charles W Caccamise succeeded as a medical examiner April 1 Dr William D Wolff who died Dec 24 1929—Dr Abraham Jablons has been appointed a lieutenant commander, medical corps U S Naval Reserve and assigned as medical officer to the thirty-second fleet division New York

Bill Enacted—S B 256 amending the Medical Practice Act by providing that an applicant for a license to practice medicine must submit evidence that he has completed not less than four satisfactory courses of at least eight months each in a medical school, has been enacted as chapter 157 of the laws of 1930 This section of the Medical Practice Act heretofore provided that an applicant for a license to practice medicine must submit satisfactory evidence that he 'had studied medicine not less than four school years including four satisfactory

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BIOCHEMICAL STUDIES ON SHOCK

II THE RÔLE OF THE PERIPHERAL TISSUES IN THE METABOLISM OF PROTEIN AND CARBOHYDRATE DURING HEMORRHAGIC SHOCK IN THE RAT *

BY JANE A. RUSSELL, PH.D., C. N. H. LONG, M.D., AND FRANK L. ENGEL,† M.D.

(From the Department of Physiological Chemistry, Yale University School of Medicine, New Haven)

(Received for publication, September 3, 1943)

In a previous report (1) it was shown that during hemorrhagic shock in the rat there is a progressive rise in the blood levels of amino nitrogen, keto acids as pyruvate, and lactate. The blood sugar falls, provided epinephrine hyperglycemia is prevented either by previous suprarenomedullation or by reduction of the liver glycogen level by fasting. These changes were interpreted as being due in part to the effects of peripheral circulatory failure on the hepatic circulation, resulting in anoxia to that organ, and in part to the effects of decreased circulation to the peripheral tissues on the metabolism of protein and carbohydrate by those tissues. Since, however, both factors undoubtedly participate to produce the changes observed in the blood, the experiments reported here were designed to analyze these changes further in terms of the relative contributions of the liver and the peripheral tissues to the total metabolic picture. By eliminating the liver surgically and then reducing the circulation by hemorrhage, it becomes possible to establish the contributions of the peripheral tissues to the biochemical changes. For this purpose rats were eviscerated, the entire gastrointestinal tract from esophagus to rectum, the spleen and the pancreas being removed, and the circulation to the liver being excluded. When shock is then induced by hemorrhage in such a preparation, any blood changes other than those produced by evisceration alone can be attributed to the effects of peripheral circulatory failure on the metabolism of the remaining tissue.

It was shown by this method that an increased rate of protein breakdown by the peripheral tissues accounts for a considerable proportion but probably not all of the observed blood amino nitrogen rise during shock, while the blood sugar, lactate, and pyruvate changes are largely determined by alterations in the metabolism of the peripheral tissues.

Methods

The methods used were the same as those described in the previous report (1, 2) with the exception that the keto acids were determined on heparinized blood, in

* Aided by a grant from the Josiah Macy Jr. Foundation

† Fellow in the Medical Sciences of the National Research Council.

mediately precipitated by 10 per cent trichloroacetic acid. Evisceration was performed by the technique used elsewhere by one of us (3). Under nembutal anesthesia a midline incision was made and double ligatures passed about the rectum, the inferior and superior mesenteric arteries, the celiac axis, and the portal vein. The rectal and arterial ligatures were tied first and then the portal, to avoid back-flow of blood into the intestines, and the entire gastrointestinal tract from rectum to esophagus, the pancreas, and spleen were removed. The esophagus was left open to permit swallowing. The operation can be performed in about 5 minutes, is associated with negligible blood loss, and postoperatively the animals show no obvious signs of shock. In the studies on blood amino nitrogen levels, rats fasted 24 hours were eviscerated 1 hour before they were subjected to a hemorrhage equivalent to 2 per cent of their body weight. For the pyruvate and lactate experiments, suprarenodemedullated rats were employed to avoid the effects of epinephrine discharge on the blood levels of these substances. Further, these animals were kept under sodium pentobarbital anesthesia for 1 hour before operation and hemorrhage was begun immediately after evisceration since these animals are known to be more sensitive to evisceration than are animals with intact suprarenal medullae.

RESULTS

The blood amino nitrogen and sugar levels were studied in a control series of nine fasted eviscerated rats and in seven fasted eviscerated rats from which blood equivalent in amount to 2 per cent of the body weight was removed 1 hour after evisceration. Fig 1 illustrates the effects of these procedures on the blood amino nitrogen levels. It will be noted that the bled rats survived approximately $2\frac{1}{2}$ hours while the control eviscerated rats survived about 5 hours. All rats died with convulsions due to hypoglycemia. In the control animals there was a progressive increase in blood amino nitrogen content amounting to 28 mg per cent in 5 hours. In the bled rats the rate of rise in amino nitrogen was identical with that in the controls during the 1st hour, but once bleeding was begun the rate of accumulation of amino nitrogen was considerably enhanced. Thus at the time of death $2\frac{1}{2}$ hours after bleeding the blood amino nitrogen had risen over 18 mg per cent, an increase not achieved in the control rats until over 4 hours had elapsed. Fig 2 shows the changes in the blood sugar levels in the same animals. While in the control animals there was a slow fall in blood sugar, hemorrhage resulted in a rapid and steady decline in blood sugar until the animals died in hypoglycemic convulsions. Indeed, it would seem that hypoglycemia was one of the limiting factors in the survival of these rats.

Since epinephrine discharge during evisceration or in hemorrhage may cause large and irregular increases in the blood sugar, lactate, and pyruvate, the blood levels of these substances were studied in rats which had been previously suprarenodemedullated. Hemorrhage was begun in these animals immediately after evisceration, blood equal in amount to $1\frac{1}{2}$ per cent of the total body weight was removed in each case. Fig 3 demonstrates the rate of fall in blood sugar in the bled and control suprarenodemedullated-eviscerated rats. Again the

very much more rapid rate of disappearance of glucose from the blood is seen in the bled rats. In Fig 4 are recorded the effects of evisceration and of

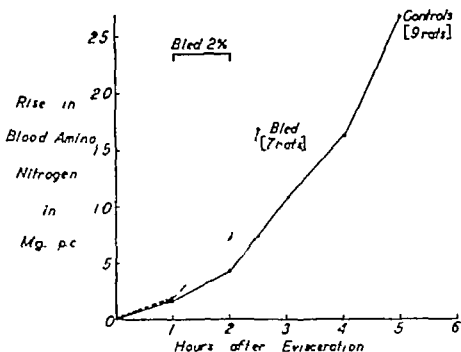


FIG 1 The effect of hemorrhage on the blood amino nitrogen content of eviscerate (functionally hepatectomized) rats. The control rats were eviscerated and the blood amino nitrogen followed until death. The bled rats were subjected to a hemorrhage equivalent to 2 per cent of their body weight between the 1st and 2nd hours after evisceration.

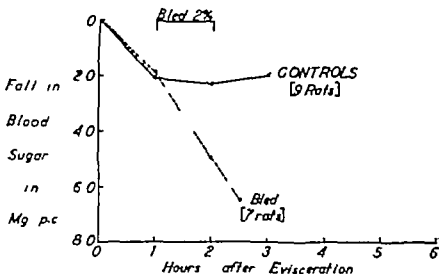


FIG 2 The effect of hemorrhage on the blood sugar levels of eviscerate rats. The rats were treated as in Fig. 1.

evisceration with hemorrhage on the blood pyruvate and lactate levels. In both series death was associated with convulsions, so that any interpretation of the changes in the terminal specimens must be made with this factor in mind. Following evisceration there was a gradual increase in the blood pyruvate in the control rats, with a parallel rise in lactate, the ratio of lactate

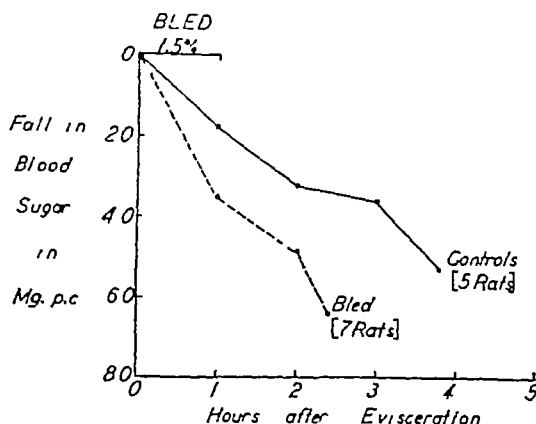


FIG 3 The effect of hemorrhage on the blood sugar levels of eviscerate supra-renalomedullated rats. The bled rats were subjected to a hemorrhage equivalent to 1.5 per cent of their body weight during the 1st hour after evisceration.

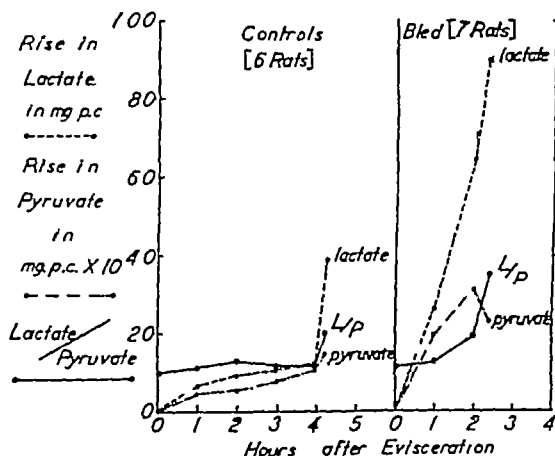


FIG 4 The effect of evisceration and evisceration plus hemorrhage on the blood lactate and pyruvate levels of supra-renalomedullated rats. The control rats were eviscerated and the blood lactate and pyruvate followed until death. The latter was associated with convulsions in all cases, which accounts for the sudden sharp rise in lactate and pyruvate terminally. The bled rats were subjected to a hemorrhage equivalent to 1.5 per cent of their body weight immediately after evisceration. Convulsions preceded death. The rats were kept under nembutal anesthesia for 1 hour before evisceration.

to pyruvate remained constant until the terminal specimens taken during convulsions, when the lactate had risen more sharply than the pyruvate. In

contrast to this was the very rapid rise in pyruvate and lactate in the bled rats, with the lactate rise outstripping the pyruvate and resulting in a mounting lactate to pyruvate ratio. Of interest was the terminal pyruvate fall at the time of the convulsions. In the control eviscerate rats the increases in blood lactate and pyruvate were small and did not approach those seen either in the intact rat subjected to hemorrhage (1), or in the bled eviscerate rat.

DISCUSSION

In the rat suffering from peripheral circulatory failure, a progressive increase in the blood amino nitrogen content is a characteristic feature. Although the method of analysis (2) is not entirely specific for amino acid nitrogen, 28 per cent of the uric acid nitrogen also being determined, all but a very small fraction of the amino nitrogen found in blood must be amino acid nitrogen. As has been pointed out elsewhere (1), appreciable and persistent elevations in blood amino acids are not seen, even after injections of relatively large amounts of these substances, unless there is impairment of liver function. Any elevation in the amino acids of the blood will depend in part on the degree of hepatic disability present and in part on the rate of amino acid production from tissue proteins or food. The rise in blood amino nitrogen in the bled rat (1) is in many cases equal to or greater than that which occurs in the liverless rat. Since in the latter case deamination is already reduced to a minimum, a greater increase in blood amino nitrogen in the shocked animals would have to be due to a greater rate of amino nitrogen production during shock. In the experiments described in this report, direct measure of this factor was obtained by comparing the rate of rise in blood amino nitrogen in the liverless rat with that in the liverless rat subjected to hemorrhage and shock. The more rapid accumulation of amino nitrogen in the blood of the bled liverless rats thus indicates an increased rate of protein breakdown in the peripheral tissues, since the viscera have been removed. Within the periods of observation in these experiments, nephrectomy does not influence the blood levels of amino acids. Amino acid excretion or deamination by the kidneys would not seem to be significant factors in the differences observed in the shocked animals. Comparison of the two curves in Fig. 1 reveals a much greater accumulation of amino nitrogen in the blood of the bled rats than in the controls in the hour and a half from the beginning of the hemorrhage, representing a considerably more rapid rate of protein breakdown in the shocked rat.

The rising blood amino nitrogen concentration during hemorrhagic shock in the otherwise normal rat may be attributed partly to increased protein degradation in the peripheral tissues and partly to failure of the liver to assimilate the amino acids resulting from this breakdown, because of the decreased blood flow to and anoxia of the liver (4). This degree of hepatic failure makes it possible to detect by study of the blood amino nitrogen level an increase in

protein catabolism which might otherwise be missed if the liver maintained its normal ability to handle large amounts of amino acids

An increase in protein catabolism after hemorrhage has previously been demonstrated by several investigators (5, 6) who studied the urinary nitrogen excretion. Similarly after trauma and burns (7) an increased nitrogen excretion has been observed. In the case of burns Glenn *et al* (8) have recently reported an increase in blood and lymph amino acid nitrogen. Our results show that the generalized tissue anoxia resulting from hemorrhage produced a rapid breakdown of peripheral tissue protein just as do burns, trauma, or local anoxia by tourniquet. In the latter cases it is probable that the increased protein catabolism is not exclusively in the traumatized tissue, but also occurs generally whenever the circulation is sufficiently depressed.

A comparison of the blood changes in sugar, lactate, and pyruvate in the eviscerate rat and the eviscerate shocked rat indicates that these changes are primarily conditioned by the state of the peripheral tissues. In the liverless preparation there is a progressive fall in the blood sugar as this substance is utilized and, as no new source is available, the animal eventually dies in hypoglycemic convulsions. The lactate and pyruvate levels slowly rise, but maintain a constant ratio to each other, except in the terminal specimen which is influenced by the effects of the convulsion. The gradual rise in these substances is probably due in part to the absence of the liver which would normally utilize lactate and pyruvate. The persistence of a normal lactate/pyruvate ratio until terminally suggests that carbohydrate is being normally metabolized by the eviscerate preparation. By comparison, in the bled eviscerate rat, glucose disappears at a much more rapid rate and lactate and pyruvate accumulate rapidly, the lactate increases in the blood faster than sugar disappears, and there is a rising lactate/pyruvate ratio. These facts suggest an increasing predominance of anaerobic over aerobic metabolism of carbohydrate in muscle (9). The more rapid disappearance of glucose in the shocked preparation may be a manifestation of the lesser efficiency in terms of energy yield of the anaerobic metabolism of carbohydrate. Since the rates of change in blood lactate and pyruvate are similar in the intact bled and the eviscerate shocked rats but are much greater than those seen in the control eviscerate rats, hepatic failure alone would not seem to be a significant factor in producing these changes during shock. On the contrary, peripheral anoxia would seem to be largely responsible.

SUMMARY

The changes in the blood levels of amino nitrogen, glucose, lactate, and pyruvate were compared in eviscerate (liverless) rats and eviscerate rats subjected to hemorrhage, in order to establish the rôle of the peripheral tissues in the blood changes during shock. It was found that —

1 The blood amino acids accumulate at a more rapid rate in the bled liverless rats than in the control liverless animals.

2 The blood sugar falls more rapidly in the liverless rat after hemorrhage, both in animals with intact suprarenal glands and those with enucleated suprarenal medullae

3 The blood lactate and pyruvate rise slowly in the liverless rat, but maintain a constant relation to each other except terminally when convulsions occur. In the bled liverless rat both lactate and pyruvate increase much more rapidly than in the control liverless rat, and the lactate/pyruvate ratio also increases

These data are interpreted to indicate that a decrease in liver function during hemorrhagic shock serves to make apparent a considerable increase in peripheral protein catabolism and accentuates the effects of an increased carbohydrate utilization by the periphery. The lactate and pyruvate changes are determined chiefly by anoxia of the peripheral tissue and probably indicate an increasing predominance of anaerobic over aerobic metabolism of carbohydrate in muscle. The liver plays a negligible rôle in the lactate and pyruvate changes in shock.

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BIOCHEMICAL STUDIES ON SHOCK

III THE RÔLE OF THE LIVER AND THE HEPATIC CIRCULATION IN THE METABOLIC CHANGES DURING HEMORRHAGIC SHOCK IN THE RAT AND THE CAT*

By FRANK L. ENGEL,† M.D. HELEN C. HARRISON § Ph.D., AND
C. N. H. LONG M.D.

(From the Department of Physiological Chemistry, Yale University School of Medicine,
New Haven)

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It has already been shown (1, 2) that certain of the changes in the metabolism of carbohydrate and protein and their degradation products during hemorrhagic shock are determined in part by alterations in hepatic function and in part by the effects of circulatory failure on peripheral tissue metabolism. In these reports it was suggested that the liver becomes less able to absorb and deaminate amino acids because of hepatic anoxia resulting from a failing oxygen supply to that organ. The experiments to be reported here are designed to show, first that there is a decreased oxygen supply to the liver during shock and that this decrease can be correlated with certain other changes occurring during shock, and secondly that diminishing the blood supply to the liver by surgical means will influence the ability of that organ to dispose of amino acids. The comparative rôles of the arterial and venous circulation to the liver for the maintenance of its function normally and during shock are also considered and quantitative data are presented concerning the liver's ability to withstand total anoxia.

Methods

Whole blood and plasma amino nitrogen levels were determined by the method of Frame, Russell, and Wilhelm (3), blood oxygen by the micro method of Roughton and Scholander (4) and expressed as per cent saturation, and hemoglobin with the Evelyn colorimeter. The blood oxygen is expressed as per cent saturation rather than content since the percentage saturation is an index of the O_2 tension in the tissues. Blood pressure in the rat was estimated by direct cannulation of the carotid artery heparin in saline being used as anticoagulant. For the cat 5 per cent sodium sulfate solution was used to prevent coagulation during blood pressure measurement from the carotid artery.

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† Fellow in the Medical Sciences of the National Research Council.

§ Alexander Brown Coxé Fellow

All experiments were carried out under sodium pentobarbital anesthesia (4 mg per 100 gm for rats and 25 to 40 mg per kilo for cats administered intraperitoneally) In those experiments in which the hepatic circulation was altered surgically no further anesthesia was given after the initial dose

The hepatic arterial circulation was occluded by ligating the celiac axis and all the branches of it which could be found While this resulted in impairment of circulation to certain other organs such as the stomach and spleen, made apparent in a few cases by slight hemorrhage into the stomach, there was never any evidence of shock in these experiments and, with a very few exceptions, all animals survived Although it is possible that some arterial circulation *via* collaterals to the liver persisted it was felt to be unlikely that they could contribute a significant amount of blood to the liver in a brief experiment

Evisceration was performed by the method described in the previous report (2)

Since it is not possible to occlude the portal vein, leaving the hepatic arterial circulation intact, without producing marked venous engorgement of the gastrointestinal tract with eventual shock, an operation was devised for the rat whereby the arterial circulation to the liver could be preserved while that by the portal vein was eliminated

In this operation the branches of the celiac axis and of the hepatic artery are tied off separately and the entire gastrointestinal tract removed with spleen and pancreas, leaving the hepatic artery patent as the only blood supply to the liver The first step is to ligate the splenic pedicle and remove the spleen Ligatures are then tied about the rectum, inferior and superior mesenteric arteries in that order The rectum and superior and inferior mesenteric arteries are then divided between ligatures and the large intestine, ileum, and jejunum gently freed At the point in the third part of the duodenum beyond which arterial circulation has been occluded a ligature is tied This point is apparent from its anemic appearance as compared to the remaining duodenum and stomach After the remaining mesentery has been ligated the intestine is divided at the above point and removed, leaving the stomach, pancreas, and part of the duodenum still to be removed The stomach is pulled down and the arteries and veins supplying the lower esophagus and the cardia of the stomach are doubly ligated and divided A hemostat is placed on the esophagus which is then divided distally The remaining mesentery to the stomach and duodenum is then ligated step by step close to these viscera and the stomach and duodenum are removed The hemostat on the esophagus is released and its lumen is reopened Any bleeding in the mesenteric stump is controlled by careful use of hemostats and by pressure. In the final steps of the operation great care must be used not to include the hepatic artery in the ligatures The portal vein and its branches should be tied off last to avoid back-flow of blood into the stomach and duodenum Since, in contrast to the other evisceration operation, slight to moderate blood loss is unavoidable, it has been found advisable to administer a small blood transfusion (1 to 3 cc depending on the amount of blood lost) immediately postoperatively to avoid the development of shock The criterion for the success of the operation, *i e*, hepatic artery patent and the absence of postoperative shock, is the fact that the nembutal anesthesia wears off and the animals exhibit normal activity The animals which failed to come out of the anesthesia or in

which more than a few tenths of a cubic centimeter of blood was found in the peritoneal cavity postoperatively were discarded. With practice the procedure can be carried out in from 10 to 20 minutes. In the studies on total hepatic anoxia the rats were prepared as above and a clamp was then applied to the celiac axis (hepatic artery) for the desired period, thereby completely occluding the blood supply to the liver.

RESULTS

The Oxygen Supply to the Liver during Shock

Since the major blood supply to the liver is by the portal vein which has been estimated to account for as much as 80 per cent of the oxygen brought to the liver under normal circumstances (5), a study was made of the oxygen saturation of portal venous blood during hemorrhage and shock in eleven rats. This was correlated with the arterial blood pressure, which can be considered as a rough measure of the arterial circulation to the liver, and with the blood amino nitrogen concentration. The latter has already been shown to be a reliable index of the degree of circulatory depression in the rat and is an indication of the rate at which the liver deals with circulating amino acids. The arterial oxygen saturation shows little change during shock except terminally (6) so it was not generally followed in the experiments on rats, although it was determined in those on cats.

In these experiments the rats were bled until the blood pressure had fallen to a desired level which varied in different animals. Fig 1 is a graphic representation of the relationship between the blood amino nitrogen levels and the portal venous oxygen saturation during hemorrhage in eleven rats. A high degree of negative correlation between the two is evident, the amino acids being high when the portal oxygen is low. Similarly, a high negative correlation is found between the arterial blood pressure and the blood amino acid concentrations, with a correlation coefficient of -0.660 in 44 determinations. Fig 7 of an earlier paper (1) demonstrates this relationship in another series of rats. The fall in portal oxygen saturation closely parallels the fall in blood pressure, as Fig 2 demonstrates. These data suggest a close relationship between the oxygen supply to the liver, as measured by the portal venous O_2 saturation and the falling blood pressure, and the failing ability of that organ to assimilate amino acids.

Since measurement of the portal venous oxygen saturation is not a convenient method of following the course of shock, simultaneous studies were made of the peripheral venous (tail vein) O_2 saturations, the portal venous O_2 saturation, the blood pressure, and blood amino acids in six rats. In another eight rats tail and portal venous O_2 saturations alone were followed during hemorrhage. Fig 3 summarizes the data on the peripheral and portal venous O_2 saturations.

Although the correlation coefficient is high ($r = +0.792$, $n = 35$), it is interesting that the correlation between the blood amino nitrogen and the tail vein oxygen is lower ($r = -0.617$, $n = 48$) than that between blood amino nitrogen and portal vein O_2 saturation ($r = -0.714$). Likewise the correlation between the tail vein O_2 saturation and the blood pressure ($r = +0.505$,

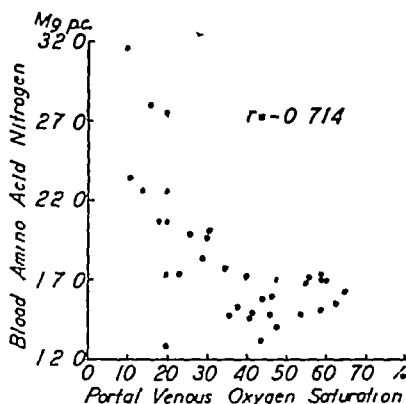


FIG 1 The blood amino nitrogen and portal venous oxygen saturation during hemorrhage and shock in eleven rats. In this and subsequent figures "r" represents the correlation coefficient.

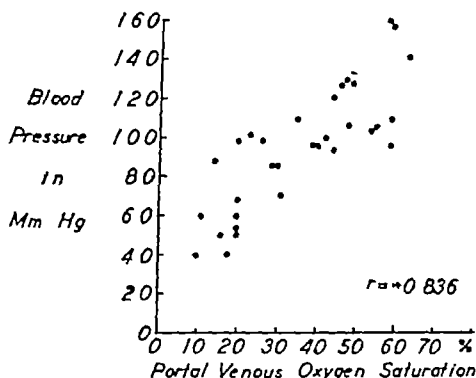


FIG 2 The arterial blood pressure and portal venous oxygen saturation during hemorrhage and shock in rats.

$n = 29$) is lower than that between the portal O_2 saturation and the B P. For practical purposes, however, the peripheral venous oxygen saturation gives a very good indication of the state of the circulation during hemorrhages as has already been suggested by several investigators (7).

Fig 4 illustrates the above relationships in two rats, in both of which it is seen that the O_2 saturation of the venous blood was a better measure of the status of the animal than was the blood pressure when both were compared to the blood

amino nitrogen. The latter we have already shown to be a very reliable prognostic index in the rat (1). In the first case (a) the blood pressure fell quite

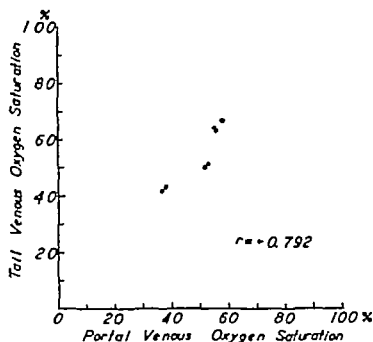


FIG. 3 The tail venous and portal venous oxygen saturations during hemorrhage and shock in rats.

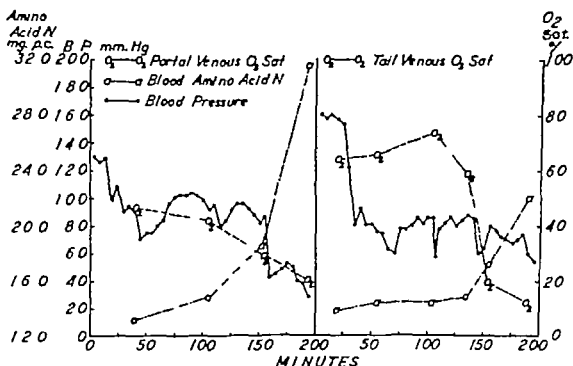


FIG. 4 The blood amino nitrogen, blood pressure, and portal and tail venous oxygen saturations in two rats subjected to fatal hemorrhagic shock.

rapidly to a level of 70 mm of Hg, but then climbed back to 90 to 100 mm of Hg, where it remained for an hour and a quarter before falling again to low levels. Nevertheless, the portal O₂ saturation was falling progressively and the amino nitrogen began to rise early, an ominous prognostic sign. In contrast is

the second rat in which the blood pressure fell to and remained at low levels while the peripheral venous O_2 saturation was maintained at a normal level for several hours and concomitantly the blood amino nitrogen showed no change. With further bleeding, however, the O_2 saturation finally fell and with this there was a sharp rise in the blood amino nitrogen and death. Most rats showed a closer correspondence between the blood pressure and venous oxygen than these two. In a few, however, the amino nitrogen seemed to follow the blood pressure closer than the venous oxygen saturation. In control experiments in which there was no bleeding, none of the blood constituents studied here showed any significant changes in periods comparable to the above experiments.

While the data on portal venous O_2 saturation and arterial blood pressure are strongly suggestive of a causal relationship between hepatic anoxia and a failure to dispose of amino acids, without measurement of the hepatic venous O_2 content the degree of hepatic anoxia could not be established with certainty. It has been shown by others (6) and confirmed by us in the rat that the arterial oxygen saturation shows little change during shock except terminally. Indeed in some cases it is still normal even at death. It is thus conceivable that an increased oxygen supply might reach the liver *via* the hepatic artery during shock to compensate for the decreased venous supply. Since it is technically very difficult to obtain hepatic venous blood from the rat, cats were used in these experiments. Further, in experiments to be described below, the effects of occlusion of the hepatic artery in the normal and shocked rat were studied in order to establish the dominant rôle of the portal vein in maintaining a normal oxygen supply to the liver.

Five cats anesthetized with nembutal were bled from the carotid artery at intervals and in such amounts as were necessary to maintain the blood pressure between 60 and 80 mm Hg for 2 to 3 hours. When the pressure fell below 60 mm. Hg and showed no evidence of a spontaneous rise blood was transfused into the femoral vein until amounts almost equal to that originally withdrawn had been replaced. In spite of this all the animals died. Samples were withdrawn at intervals from the carotid artery, femoral vein, portal vein, and hepatic vein for measurement of the oxygen saturation while the plasma amino acid level was also determined on the arterial blood. Fig 5 shows the results of a typical experiment. Here it is seen that the arterial O_2 was maintained at normal levels as long as it was followed, while the venous O_2 saturations fell early reaching very low levels. In this particular case the hepatic venous O_2 saturation had fallen to 22 per cent in an hour, when the B. P. had reached 80 mm. Unfortunately no further hepatic vein samples were taken from this cat. However, a similar early fall occurred in other cats and was progressive. In two cats it reached 0 and 3 per cent at 30 and 20 minutes respectively before death (Table I). This striking degree of oxygen unsaturation indicates a very low level of oxygen available to the hepatic tissue. In most cases, the femoral vein O_2 fell more rapidly than the portal vein O_2 suggesting that peripheral vasocon-

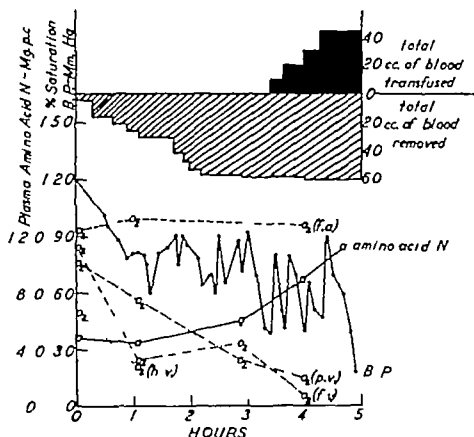


FIG 5 The effect of hemorrhage and shock on the plasma amino nitrogen, blood pressure, and oxygen saturation in the femoral artery (f.a.), the femoral vein (f.v.), the portal vein (p.v.) and the hepatic vein (h.v.) in a 2.3 kilo cat.

TABLE I

Blood pressure	Oxygen as per cent saturation				Plasma amino acid N
	Femoral artery	Femoral vein	Portal vein	Hepatic vein	
mm Hg					mg per cent
190*	99	80	56	59	5.8
130*	82	75	68	45	4.2
144*	87	69	76	74	5.6
115*	92	89	77	50	4.8
114*	84	70	66	77	4.9
104	100	19	18	21	7.6
84	98	43	12	0	4.8
80	99	22	56	22	4.3
70	—	34	26	—	6.0
70	95	28	40	30	6.0
60	—	3	—	—	11.8
50	95	7	—	—	8.9
50	—	—	14	—	11.3
50	85	5	16	3	7.4
40	90	21	18	11	6.2
50	—	—	—	—	8.0
40	—	—	—	—	8.7
30	—	—	—	—	7.8

* Initial specimens.

striction was a significant factor. This is further borne out by one cat whose blood pressure was well maintained despite hemorrhage but whose venous oxygen saturation had fallen to 20 per cent 1 hour after bleeding was begun. The amino nitrogen rise in the plasma occurs somewhat later than in the rat and is not as striking in degree. Since the metabolic rate per unit weight in the cat is slower than in the rat it seems likely that the difference in degree between the amino nitrogen rise in the cat and rat may be due to a slower rate of peripheral protein breakdown by the former. This is borne out by the fact that following complete elimination of the liver from the circulation by evisceration the rise in blood amino acids in the cat is much more gradual than in the rat (8). Table I summarizes the data on the five cats.

*The Effect of Restriction of Hepatic Blood Supply
on the Blood Amino Nitrogen Levels*

It has now been shown that shock is associated with a marked decrease in oxygen supply to the liver and with this there is a rise in the blood amino nitrogen. In order to demonstrate that there is a causal relationship between the decrease in O_2 supply to the liver because of shock and the rise in amino nitrogen, experiments were devised to show whether decreasing the blood supply to the liver by surgical means would also cause a rise in the blood amino acids. For this purpose the behavior of the blood amino nitrogen was compared under circumstances in which the liver received blood only through the portal vein, or only through the hepatic artery, or in which the hepatic circulation was completely occluded for varying periods of time.

(a) The Portal Vein as Sole Blood Supply. Hepatic Artery Ligation —

Although various investigators have disagreed as to whether the hepatic arterial supply to the liver is essential to its function, most are in agreement that the major blood supply to the liver is *via* the portal vein (9). Our data suggest that changes in the portal circulation are of major importance in influencing liver function during shock and that the hepatic artery plays only a minor rôle. In Fig. 6 are recorded the effects of hepatic artery ligation on the levels of the blood amino nitrogen in twelve normal rats which were examined up to 24 hours postoperatively. It will be noted that this procedure had no effect on the ability of the liver to handle amino acids. These rats survived indefinitely, with the exception of two that developed an intestinal obstruction postoperatively.

Although this procedure had no effect on the normal rat, it was thought possible that if a strain were put on the circulation by subjecting the animal to a hemorrhage which would have little or no effect on the blood amino nitrogen of the normal rat, the rats with ligated hepatic arteries would show a rise in blood amino nitrogen if the hepatic arterial blood were an essential factor in protecting

the liver Fig 6 shows that there is no significant difference between the blood amino nitrogen levels of six normal and seven hepatic artery ligated rats after a hemorrhage equivalent to 2 per cent of the body weight. These experiments were all performed immediately after ligation so that the likelihood of there being very active collateral arterial circulation to the liver is not great.

(b) *Hepatic Artery As Sole Blood Supply*—

The liver whose sole blood supply is by the portal vein would thus seem to be quite competent to deaminate amino acids at a normal rate and to have as great a margin of safety as the normal liver in the rat. That being the case, it was of interest to determine whether the liver which receives blood only from the hepatic artery can maintain its function. For this purpose an operation was

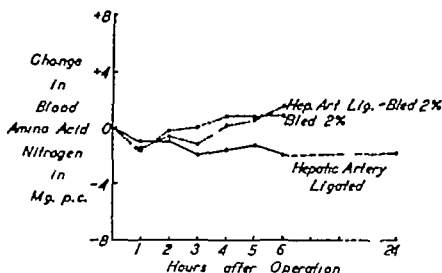


FIG 6 The effect of hepatic artery ligation on the blood amino nitrogen of nine normal rats and of seven rats subjected to a hemorrhage equivalent to 2 per cent of the body weight as compared to six normal rats bled the same amount

devised whereby the viscera were removed along with the portal vein, while the hepatic artery was left intact and patent. This operation has been described under the section on methods. It is, of course, realized at the outset that such an animal lacking viscera including pancreas is not normal and any results from it must be interpreted with caution. These animals recover from the operation and live as long as 36 hours, eventually succumbing to peritonitis and diabetes. The blood sugar usually reaches 200 or more mg per cent after 24 hours. Nevertheless it is felt that observations on the blood amino nitrogen of these rats may be a valid indication of liver function during the first 7 hours post operatively, provided care is taken to prevent postoperative shock by transfusion and provided only those animals are used which survive at least 15 to 20 hours. When the blood amino nitrogen levels of these rats are compared to hepatic artery ligated rats and totally eviscerated rats (functionally hepatectomized) (Fig 7) it is seen that the hepatic artery alone can maintain hepatic

function for some hours, since the rise in amino nitrogen is slight, although definitely greater than the normal. Furthermore, in contrast to the eviscerate rat in which the amino nitrogen rises rapidly and the animal fails to come out of the nembutal anesthesia, rats in which the hepatic artery alone is patent regain consciousness postoperatively. But while this rat retains considerable ability to dispose of amino acids, its margin of safety is very small. Only a small amount of hemorrhage with resultant fall in blood pressure and flow causes a rapid rise in the blood amino nitrogen. This is to be compared to the situation in the hepatic artery ligated rats which could stand a 2 per cent hemorrhage

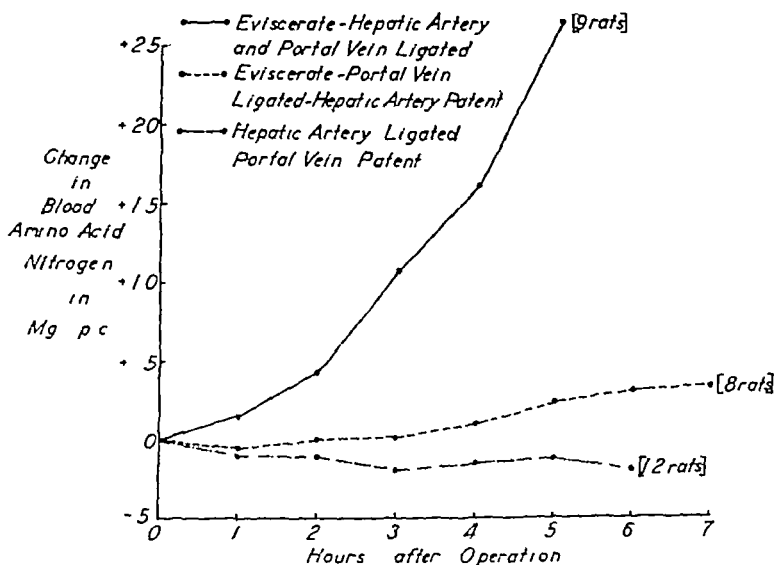


FIG 7 The comparative effects on the blood amino nitrogen of the rat of complete exclusion of the hepatic circulation, of exclusion of the portal circulation, and of exclusion of the hepatic arterial circulation

without causing a greater than normal rise in blood amino nitrogen. Decreasing the blood supply of the liver below that contributed by the hepatic artery normally results in a decreased ability by the liver to dispose of circulating amino acids.

(c) *Effect of Complete Occlusion of Hepatic Circulation for Various Periods —*

The experimental results so far described indicate that amino acids accumulate in the blood if the blood flow to the liver is sufficiently reduced, as it may be during shock. But they do not demonstrate whether this phenomenon during shock is prehepatic, *i.e.*, that hepatic blood flow is so impaired that amino acids are supplied to the liver at a slower rate than normal even though they

may be produced abnormally rapidly in the periphery (2) or whether it is intrinsically hepatic, *i.e.*, the liver loses its ability to take up or deaminate amino acids because of anoxia. By use of the preparation in which the liver receives its blood supply only through the hepatic artery this question was subjected to analysis. Rats were prepared as described above, a small bulldog clamp was placed on the hepatic artery for 15, 30, 45, 60, 90, and 120 minutes and the blood amino nitrogen levels followed for 7 hours. In all cases the rats came out of the anesthesia after the clamp was removed, but the period for which anesthesia persisted depended on how long the hepatic circulation was

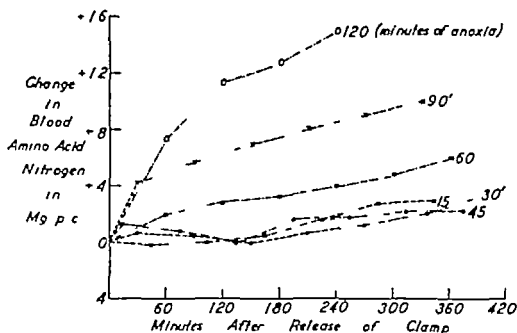


FIG 8 The effect of complete occlusion of the hepatic circulation for 15 to 120 minutes on the blood amino nitrogen levels of the rat. Note that with less than 60 minutes of anoxia the liver subsequently is able to clear amino acids from the blood as well as the control, plotted in Fig 7 (eviscerate-portal vein ligated hepatic artery patent)

occluded. On clamping the artery the liver became deeply cyanotic and there was no evidence from its appearance that any circulation persisted. On releasing the clamp the normal color of the liver reappeared slowly and in an irregular manner. In those in which the circulation was obstructed for 30 minutes or more gross infarcts could be seen but the major bulk of the liver showed a normal color. Microscopically, small to large infarcts could be found in all the livers in which the hepatic artery was the sole remaining source of blood even when the artery was not occluded at all. All the rats reported here survived at least 12 hours and many, including those totally anoxic for 60 minutes or more, lived 24 or more hours postoperatively. The results (Fig 8) show that the liver can be subjected to a considerable period of anoxia before its ability to handle amino acids is irreversibly damaged. When the liver circula

tion is occluded for 30 minutes or more, amino acids increase in the blood during the 1st hour, but in the case of the 30 minute and 45 minute occlusion this is apparently an accumulation taking place while the liver is out of the circulation because on release of the clamp the blood amino nitrogen returns to the control level in the subsequent hours. With 1 hour of anoxia, however, a definite break occurs. The amino nitrogen of the blood rises progressively indicating intrinsic damage to the deaminating mechanism of the liver after this amount of anoxia in this particular preparation.

DISCUSSION

The material presented in this series of papers would suggest that a combination of extrinsic and intrinsic factors determine hepatic function during peripheral circulatory failure. Other workers have published data indicating that the hepatic circulation fails in shock. Blalock and Levy (10) noted a 53 per cent decrease in portal blood flow in dogs after only a moderate hemorrhage. McMichael (5) during the course of his studies on the oxygen supply of the liver in the cat comments on the decrease in portal and hepatic venous oxygen contents in those animals which were failing. Wood *et al* (11) reported a low portal vein oxygen content in dogs after hemorrhage. The decrease in oxygen supply to the liver of the rat and cat during shock is confirmed in the present report and its relation to hepatic function is made clear by the high degree of correlation between the fall in portal venous oxygen saturation and fall in blood pressure and the rise in the blood amino acids.

The low hepatic vein oxygen saturation in shock is indirect evidence that the hepatic circulation as a whole is reduced, and the data suggest that any compensatory rôle by the hepatic artery in maintaining the blood flow to the liver during shock is not adequate. In the literature (9) there is still considerable disagreement on how essential the hepatic artery and portal vein are respectively to the integrity of the liver. The fact that ligation of the hepatic artery of the rat does not influence the blood amino acids either in an otherwise normal rat or in one subjected to a small hemorrhage when compared to a normal or bled control indicates that, in this species at least, the hepatic artery is not essential to the hepatic function of the metabolism of amino acids. In contrast, on elimination of the portal vein, this ability of the liver is just barely maintained and any reduction in the arterial blood flow because of hemorrhage elsewhere results in a rapid rise in blood amino acids. It would thus appear probable that in shock the portal venous circulation is the main determining factor in the ability of the liver to clear amino acids from the blood and that the hepatic artery cannot play a very significant rôle in compensating for portal venous insufficiency due to shock.

Although it seems that the hepatic circulation in shock may be sufficiently depressed to account for a prehepatic accumulation of amino acids in the blood,

the experiments on the complete occlusion of the liver circulation show that if anoxia is sufficiently prolonged irreversible damage takes place. What functions other than those of handling amino acids are damaged and how soon are not yet known. That the liver is damaged during shock is suggested in many studies on the pathology of both clinical and experimental shock (12), but in general few studies of liver function have been made during the course of shock. Similarly under the conditions of the experiments reported in these papers there is evidence that the degree and duration of anoxia is sufficient to damage the liver. Russell, Long, and Wilhelm, in the paper to follow (13), show that there is a significant depression in the oxygen consumption of liver slices from shocked rats. The decrease in oxygen consumption correlates well with the degree of shock as measured by the blood amino nitrogen levels. Further, as will be reported later (14) there is a profound change in the electrolyte pattern of the liver in severe shock due to hemorrhage. This is similar to that which has already been reported by Clarke and Cleghorn (15) after traumatic shock in the rat.

With respect to protein and amino acid metabolism the course of events during peripheral circulatory failure may be visualized as follows. By mechanisms varying in different types of shock the circulating blood volume is decreased and with this there is a diminution in blood flow. This results in a diminished supply of oxygen to the tissues, the first of which to be affected are probably the peripheral tissues, particularly the extremities, and the liver. An increased rate of peripheral protein breakdown ensues from the anoxia and the amino acids and other products resulting therefrom begin to accumulate in the blood since they either are not taken up or are not deaminated sufficiently rapidly by the liver. If the hepatic anoxia persists long enough actual damage to the liver probably occurs and this organ then begins to lose its ability to deal with even those amino acids that pass through it. One may speculate on a possible relation between this stage and the so called irreversible phase of shock but further study is necessary to clearly establish this relationship. As has already been indicated in the previous paper, the fall in blood sugar and the mounting blood lactate, pyruvate, and lactate/pyruvate ratio are manifestations of peripheral anoxia rather than an indication of hepatic insufficiency.

SUMMARY

1 In a series of rats subjected to hemorrhage and shock a high negative correlation was found between the portal and peripheral venous oxygen saturations and the arterial blood pressure on the one hand, and the blood amino nitrogen levels on the other, and a high positive correlation between the portal and the peripheral oxygen saturations and between each of these and the blood pressure.

2 In five cats subjected to hemorrhage and shock the rise in plasma amino

nitrogen and the fall in peripheral and portal venous oxygen saturations were confirmed. Further it was shown that the hepatic vein oxygen saturation falls early in shock while the arterial oxygen saturation showed no alteration except terminally, when it may fall also.

3 Ligation of the hepatic artery in rats did not affect the liver's ability to deaminate amino acids. Hemorrhage in a series of hepatic artery ligated rats did not produce any greater rise in the blood amino nitrogen than a similar hemorrhage in normal rats. The hepatic artery probably cannot compensate to any degree for the decrease in portal blood flow in shock.

4 An operation was devised whereby the viscera and portal circulation of the rat were eliminated and the liver maintained only on its arterial circulation. The ability of such a liver to metabolize amino acids was found to be less than either the normal or the hepatic artery ligated liver and to have very little reserve.

5 On complete occlusion of the circulation to the rat liver this organ was found to resist anoxia up to 45 minutes. With further anoxia irreversible damage to this organ's ability to handle amino acids occurred.

6 It is concluded that the blood amino nitrogen rise during shock results from an increased breakdown of protein in the peripheral tissues, the products of which accumulate either because they do not circulate through the liver at a sufficiently rapid rate or because with continued anoxia intrinsic damage may occur to the hepatic parenchyma so that it cannot dispose of amino acids.

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BIOCHEMICAL STUDIES ON SHOCK

IV THE OXYGEN CONSUMPTION OF LIVER AND KIDNEY TISSUE FROM RATS IN HEMORRHAGIC SHOCK *

By JANE A. RUSSELL PH D., C. N. H. LONG M D, AND
ALFRED E. WILHELMI PH.D

(From the Department of Physiological Chemistry, Yale University School of Medicine,
New Haven)

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In the preceding papers of this series (1-3) it has been indicated that one of the consequences of hemorrhagic shock in the rat is a failure of hepatic function due to diminished blood flow and oxygen supply to the liver. The object of the experiments reported in this paper was to examine the effects of hemorrhage on the liver and kidney more directly by comparing the rates of respiration of liver and kidney slices from normal rats and from rats in progressively severe states of shock. In addition, experiments were carried out to test how far any tissue changes taking place after hemorrhage might be accounted for simply by anoxia.

Methods and Materials

Male albino rats of the Sprague-Dawley strain, weighing 250 to 300 gm., were used throughout these experiments. The animals were fed a diet of purina dog chow and in all instances were fasted for 24 hours before being studied. All experiments were performed under light anesthesia with sodium pentobarbital (nembutal) administered intraperitoneally in a dose of 4 mg per 100 gm.

Shock was induced by bleeding from the cut tail. An amount of blood equivalent to 3 per cent of the body weight was removed, usually over a period of 1 hour. The animal was kept warm under a lamp and at the end of an hour after bleeding (or earlier, if the animal appeared to be near collapse) the liver and in some experiments the kidneys were excised, washed free of blood, blotted upon a hardened filter paper, and placed in a covered dish on ice. In some experiments, samples of blood were taken at the onset of bleeding and again just before the animal was sacrificed in order to determine the blood amino nitrogen. Normal control animals were kept under anesthesia for periods comparable to those endured by the bled rats.

The respiration of thin slices of the liver and kidney tissue was studied in the Warburg apparatus. The duration of these experiments was 2 hours, the temperature was 37.5°C., and the vessels were filled with oxygen. The main chamber of each vessel contained 2.5 ml. of the "physiological salt solution" of Krebs (4) buffered with phosphate, pH 7.4. The side bulbs contained 0.5 ml. of the buffer solution, either plain or containing suitable amounts of glucose, sodium succinate (neutral), or

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liver *Kochsaff*, as the design of the experiment required. These additions were tipped in at the end of a 15 minute equilibration period, so that the operating volume for the experiments was 3.0 ml. Carbon dioxide was absorbed in 0.1 ml of 30 per cent potassium hydroxide placed in the central well of each vessel.

All of the tissue required for a single experiment (usually enough to serve 12 vessels and to provide parallel samples for dry weight determinations) were quickly sliced by hand, by the method of Deutsch (5), and collected in a Petri dish with a slotted top, lined with moistened filter paper, and cooled with ice. This cold moist chamber keeps the tissue in good condition and prevents any marked changes in the original water content of the tissues. From this pool of slices samples of about 200 mg weight were measured on a torsion balance and placed in the Warburg vessels. Five smaller samples of 50 to 100 mg were weighed and placed in tared vials to be dried in the oven at 110°C for the determination of initial dry weight. After the tissues were distributed, the vessels were attached to their manometers, filled with oxygen, mounted in the bath, and shaken for a 15 minute equilibration period at 100 to 110 double excursions per minute.

In the experiments in which the effects of anoxia *in vitro* were studied, liver or kidney slices from a normal fasted rat were weighed and distributed in 12 vessels as described above. Four vessels were filled with oxygen, the remaining 8 with nitrogen and all were placed in the bath and shaken for 15 minutes. Four of the nitrogen-filled vessels were then removed, refilled with oxygen, and replaced in the bath. At the end of another 15 minutes, the taps of the 8 vessels now filled with oxygen were closed and the measurement of the respiration in these vessels was begun. After 1 hour, the 4 remaining nitrogen-filled vessels were removed from the bath, refilled with oxygen, and replaced. At 1 hour, 15 minutes, the taps of these vessels were closed and the respiration was measured for the ensuing hour. At this time, additions were made from the side bulbs of all the vessels, and the effects of the additions on the oxygen uptake were measured for another hour. The duration of these experiments was 3 hours, 15 minutes, and the tissues were equally disposed (a) in oxygen continuously, (b) in nitrogen for 15 minutes, then in oxygen, or (c) in nitrogen for 60 minutes, then in oxygen.

In some experiments the final dry weight of the tissues was determined. The slices of 5 vessels were removed, washed briefly in distilled water, blotted on a No. 1 Whatman filter paper, placed in tared vials, and dried in the oven at 110°C.

Liver *Kochsaff* was prepared by mincing several livers of fed normal rats, suspending the mince in 5 times its weight of distilled water, and heating the mixture to 80 to 90°C for 10 minutes. The cooked material was chilled and thoroughly centrifuged, and the supernatant solution was frozen and dried in the lyophil apparatus. A fluffy, soluble, yellow powder was obtained which could be conveniently weighed out and dissolved in the buffer solution used in these experiments. In each instance an amount of *Kochsaff* was taken which was equivalent to the weight of liver tissue slices which it was intended to reinforce. This was calculated from the yield of dry material extracted from the livers. In these experiments it amounted to about 10 mg of the powder for each 200 mg sample of liver slices.

Blood amino nitrogen was determined by the method of Frame, Russell, and Wilhelm (6) on 0.2 ml samples of whole blood. Oxygen uptakes are expressed as " Q_{O_2} ", cubic millimeters of oxygen per milligram initial dry weight of tissue per hour.

The initial dry weights were calculated from the weights of the samples and the per cent dry weight of the parallel tissue samples taken at the beginning of the experiment.

RESULTS

Although the standard bleeding procedure did not produce a uniform degree of shock in the experimental animals every bled rat exhibited some signs of shock in the period after bleeding. By observations of pallor, cyanosis, depth and rate of respiration, depth of anesthesia, and ease of bleeding, the animals could be classed as being in good, fair, or poor condition at the time the tissues

TABLE I
Oxygen Utilization of Liver Slices from Bled Rats

Condition	Normal rat controls —		Bled rats					
			I (good)		II (fair)		III (poor)	
	—		+1.7		+3.0		+7.2	
Increase in blood amino N mg. per cent	No.	QO ₂	No.	QO ₂	No.	QO ₂	No.	QO ₂
No substrate								
1st hr	25	5.60 ± 0.10	16	5.00 ± 0.16	14	3.63 ± 0.17	12	1.82 ± 0.08
2nd hr	25	4.69 ± 0.10	16	4.05 ± 0.13	14	2.83 ± 0.14	12	1.30 ± 0.09
Glucose, 0.1 per cent								
1st hr	28	5.39 ± 0.13	19	5.00 ± 0.14	23	3.60 ± 0.12	24	1.92 ± 0.03
2nd hr	28	4.51 ± 0.12	19	4.10 ± 0.13	23	2.90 ± 0.10	13	1.23 ± 0.04
Glucose, 0.1 per cent, <i>Kochsolt</i>								
1st hr	8	5.4 ± 0.2	2	6.0 ± 0.2	4	3.6 ± 0.1	6	2.3 ± 0.3
2nd hr	8	4.3 ± 0.2	2	4.7 ± 0.2	4	2.8 ± 0.1	6	1.5 ± 0.2
Succinate, 0.01 M								
1st hr	19	10.05 ± 0.18	19	9.58 ± 0.14	11	7.93 ± 0.22	8	7.28 ± 0.14
2nd hr	19	8.46 ± 0.16	19	4.60 ± 0.13	11	2.93 ± 0.16	8	1.54 ± 0.17
Succinate, 0.04 M								
1st hr	6	17.6 ± 0.1			6	18.8 ± 0.2	3	20.3 ± 0.4
2nd hr	6	9.3 ± 0.2			6	6.3 ± 0.2	3	3.3 ± 0.1
Succinate 0.04 M, <i>Kochsolt</i>								
1st hr	6	18.4 ± 0.5			6	19.3 ± 0.3	3	21.5 ± 0.4
2nd hr	6	10.2 ± 0.7			6	8.0 ± 0.2	3	5.1 ± 0.2

were taken. These appraisals were supported by the determinations of the rise in blood amino nitrogen, the extent of which is proportional to the severity of shock (1).

The oxygen uptake of the liver tissue of bled rats exhibited a mild (but significant), moderate, or profound depression, in accordance with the estimates of the rat's condition and the increases in the blood amino nitrogen. The presence or absence of glucose as substrate had no influence on the oxygen uptake of liver slices either from normal rats or from rats in states of shock. The data are presented in Table I. The inverse relationship between the QO₂ of the liver tissue and the increase in the blood amino nitrogen is shown in Fig. 1.

The depressed respiration of the liver slices after hemorrhage was not a con

sequence of prolonged subnormal body temperature, since the rectal temperature of most of the animals was maintained throughout the period of observation. The depression in oxygen uptake of the liver tissue was correlated only with the severity of shock, and not necessarily with the speed with which the animals were bled or with the rapidity with which the symptoms developed after bleeding.

Since one of the important factors in maintaining normal tissue respiration is the concentration of coenzyme substances, a series of experiments was carried out to test whether the low rate of respiration of liver tissue after hemorrhage might not be due to a deficiency of these agents. The effects on the liver slices of the addition of liver *Kochsäft* in amounts equivalent to the size of the

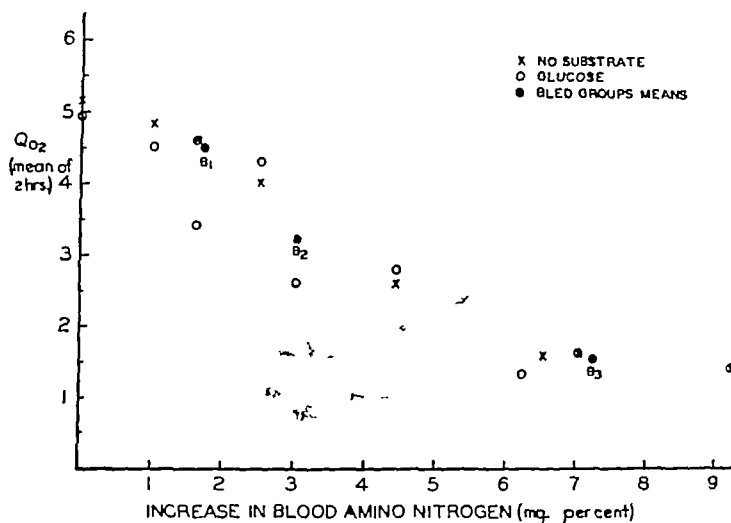


FIG 1

tissue sample taken were studied in a group of normal and bled rats. The data (Table I) indicate that the supplement of soluble coenzyme factors had little or no effect on the level of the oxygen uptake of liver slices from normal rats or from animals in moderate or severe states of shock, but that there was a strong suggestion of improvement in the performance of the liver tissue from bled rats in "good" condition. Loss or destruction of coenzyme factors after hemorrhage might therefore contribute in part to the depression of liver respiration, but it is evidently not the sole cause of the depression.

Succinate was selected as a test substrate in another series of experiments because it is readily oxidized by normal tissues, and because the complex succinoxidase system may play an important part in the normal respiration of the tissues. The oxygen uptakes of liver slices from a number of normal and bled rats, in the presence of 0.01 M and of 0.04 M succinate, are presented in Table I.

With 0.01 M succinate, the levels of oxygen uptake of the different classes of tissue differ in the same order as they do in the absence of substrate, the increment in oxygen uptake over the no-substrate level during the first hour is in every instance nearly the same (normal, +4.4, class I, +4.6, class II, +4.3, class III, +5.4). In the 2nd hour the respiration of all classes has returned to the no-substrate level. The increased respiration with succinate has therefore not resulted in improvement or repair of the basal respiration of the liver tissue from the bled rats.

The responses of the tissues to 0.04 M succinate are somewhat different. In the 1st hour, there is a greater oxygen uptake by the liver slices from the bled rats, and if the increments over the no-substrate levels are taken, the increases in oxygen uptake are significantly greater in the liver tissue from the bled rats.

TABLE II
Percentage Dry Weight of Liver and Kidney Slices from Normal and Bled Rats

	Dry weight			
	No	Initial	No	Final
		<i>per cent</i>		<i>per cent</i>
Liver				
Control	24	27.7 \pm 0.2	3	17.0 \pm 0.8
Bled (I)	5	27.7 \pm 0.5	—	
(II)	7	26.7 \pm 0.4	2	16.6
(III)	6	25.7 \pm 0.4	1	13.6
Kidney				
Control	4	23.9 \pm 0.3		
Bled (I)	1	25.0		
(II)	2	23.3		
(III)	1	23.1		

(normal, +12.8, class II, +15.7, class III +20.7). This may be an expression of a tendency towards disorganization of the liver tissue from bled rats. It is well known that the rate of oxidation of succinate is greatly increased by mincing or homogenizing the tissue. An effect of moderate or profound shock upon the integrity of the liver is indicated by the data on the initial and final dry weights of the tissues (Table II). The original water content of the liver increases steadily with increasing severity of shock, and the final dry weights suggest that the liver slices from the bled rats lose more substance during the experiments than liver slices from normal rats. It is difficult to decide whether this is a consequence of, or a factor contributing to, the low rates of respiration of liver tissue from bled animals. The data do suggest that the initial dry weight is a somewhat safer measure of the comparative activities of different tissue samples than the dry weight based upon the amount of tissue recovered from the vessels at the end of the experiments. The effects of liver *Kochsäft* on

the oxygen uptake of the various classes of liver tissue in the presence of 0.04 M succinate are not significant in the 1st hour. In the 2nd hour, however, the oxygen uptake of the liver slices from the bled rats was better maintained in the presence of *Kochsalf*.

The experiments with succinate indicate that there is little or no impairment of the succinoxidase system in the liver tissue of rats in hemorrhagic shock. With both concentrations of succinate the course of the respiration was nearly the same in all classes of liver tissue, and the same maximum rates were attained in the first few minutes after the addition of the substrate. The low rates of respiration of rat liver tissue after hemorrhage cannot be ascribed to the development of defects either in the cytochrome system or in the succinic dehydrogenase.

TABLE III
Oxygen Utilization of Kidney Slices from Bled Rats

Condition	Normal rat controls		Bled rats					
			I (good)		II (fair)		III (poor)	
	No	QO ₂	No	QO ₂	No	QO ₂	No	QO ₂
No substrate								
1st hr	4	16.1	2	15.4	4	16.5	2	14.3
2nd hr	4	13.9	2	13.1	4	14.0	2	13.0
Glucose, 0.1 per cent								
1st hr	5	15.9	2	15.3	6	17.7	2	14.9
2nd hr	5	15.0	2	14.4	6	16.2	2	14.1

The effects of hemorrhage upon the oxygen uptake of rat kidney tissue are relatively small. In Table III, it will be seen that kidney slices from rats even in profound shock exhibit only a slight depression in rate of oxygen consumption. With glucose the initial rate of respiration is better maintained in all classes of kidney tissue.

In hemorrhage shock in the rat there is a sharp reduction in the portal blood flow and oxygen supply (3). In these circumstances the liver, which receives a large part of its oxygen supply by the portal vein, may be subjected to severe anoxia. It therefore seemed of interest to compare the effects of lack of oxygen *in vitro* on the respiration of normal rat liver slices with the effects of hemorrhage. In Table IV are presented the results of experiments in which normal rat liver slices were exposed to nitrogen at 37.5°C for 15 minutes and 60 minutes. The effects of this treatment on the oxygen uptake are quantitatively and qualitatively similar to the effects of moderate and severe shock after hemorrhage. The succinoxidase system appears to be relatively unaffected in these experiments, and there is a slight improvement in the respiration of the anoxic

TABLE IV

The Effect of Anoxia in Vitro on the Oxygen Uptake of Liver Slices of Fasted Rats (Glucose 0.2 Per Cent Present in All Vessels)

1st hr	Oxygen throughout		Nitrogen 15 min., then oxygen		Nitrogen 60 min., then oxygen	
	No	QO ₂	No.	QO ₂	No	QO ₂
2nd hr	14	4.69 ± 0.13	12	3.05 ± 0.11	11	1.45 ± 0.06
3rd hr						
No addition	3	4.7	3	2.7	3	0.9
Kochsast added	5	4.8	4	3.4	4	1.4
Succinate, 0.02 M	4	12.4	3	12.4	3	11.9

TABLE V

The Effect of Kochsast and Anoxia on the Oxygen Uptake of Rat Liver Slices (in 0.2 Per Cent Glucose)

	Oxygen throughout	Nitrogen 15 min. then oxygen	Nitrogen 60 min., then oxygen
	QO ₂	QO ₂	QO ₂
No addition			
1st hr	5.4	3.2	—
2nd hr	5.3	2.9	1.5
3rd hr	4.9	2.6	0.9
Kochsast added			
1st hr	5.2	4.9	—
2nd hr	5.0	3.9	2.3
3rd hr	4.6	3.5	1.4

These figures were obtained simultaneously on slices from the liver of one fasted rat. Each figure is the mean of closely agreeing duplicate determinations.

TABLE VI

The Effect of Anoxia in Vitro on the Oxygen Uptake of Rat Kidney Slices

	Oxygen throughout	Nitrogen 15 min. then oxygen	Nitrogen 60 min., then oxygen
	QO ₂	QO ₂	QO ₂
No substrate			
1st hr	17.1	14.3	—
2nd hr	14.5	13.5	5.6
3rd hr	12.3	11.5	4.2
Glucose 0.1 per cent			
1st hr	17.7	14.8	—
2nd hr	16.3	15.5	10.0
3rd hr	15.3	14.7	10.4

Each figure is the mean of 4 determinations which agreed closely

tissue in the presence of *Kochsaff*. The data of a single experiment in Table V illustrate more clearly the course of the respiration and the effects of *Kochsaff*.

The data of a similar series of experiments with rat kidney slices are presented in Table VI. The effects of the shorter period of anoxia are much less marked in kidney tissue than in liver tissue, but after 60 minutes in nitrogen, the respiration of both tissues is depressed in about the same proportion. Glucose, which is without effect on the oxygen uptake of liver slices, supports nearly complete recovery of the oxygen uptake of kidney slices after 15 minutes in nitrogen, and nearly doubles the rate of respiration of kidney tissue after 60 minutes in nitrogen. The more moderate effects of hemorrhage upon the rate of oxygen consumption of rat kidney tissue may therefore be due to the fact that the blood flow and oxygen supply to this organ are not so severely diminished as compared to the liver, and to the fact that, by using glucose more readily, the kidney is better able to withstand and overcome the effects of anoxia.

DISCUSSION

The data presented here indicate that the respiration of liver tissue is severely depressed in shock following hemorrhage in the rat, and that this change may be largely a consequence of lack of oxygen. The blood chemical changes in the bled rat described in earlier papers of this series (1-3) also indicate that an important metabolic factor in hemorrhagic shock in the rat is a decrease in hepatic function due to diminished blood flow and oxygen supply to the liver. The behavior of the isolated tissue provides a direct confirmation of the other evidence showing that the liver is seriously affected in hemorrhagic shock. The most consistent sign of hepatic failure is the rise in blood amino nitrogen, which can now be correlated with blood pressure (1), venous oxygen tension (3), and rate of oxygen uptake of the liver tissue *in vitro*.

The nature and sequence of the effects of hemorrhage and anoxia upon the respiration of liver tissue remain to be explained. From the experiments with *Kochsaff* it is suggested that one of the first effects is the loss or partial destruction of one or more coenzyme factors necessary for normal tissue function. The failure of the supplement of *Kochsaff* to increase the rate of respiration of liver tissue from moderately or profoundly shocked rats indicates that enzyme systems as well as coenzymes may become disorganized as shock progresses, but the primary loss or breakdown of coenzymes essential to the production and transfer of energy within the cell may influence critically the rate of decline of other tissue functions.

The experiments with succinate indicate that an increased rate of oxygen uptake in the tissue following the addition of a readily oxidizable substrate does not of itself lead to an improvement in the basal rate of respiration. In every instance, the terminal rate of respiration of the tissue to which succinate had

been added was identical with the rates of oxygen uptake of the slices respiring without added substrate. Thus, although the oxidation of succinate has been linked with phosphorylation of glucose (7) and may be regarded as an energy producing reaction, there is in these experiments no evidence that the energy has been used to restore the conditions for normal basal respiration. It may be significant that the combination of succinate and *Kochsäft* did result in better maintenance of the respiration of liver tissue from shocked animals in the period following the complete oxidation of succinate to fumarate. Both the extra supplement of coenzyme factors and the increased rate of energy production may be required to initiate the restoration of normal tissue respiration.

The apparent integrity of the succinoxidase system suggests that the ability to take up oxygen and to carry out the terminal steps of hydrogen and electron transport is not a limiting factor in the respiration of liver tissue from rats in states of shock. In drawing this inference from the behavior of isolated tissues a note of caution is required. The oxidation of succinate proceeds vigorously in minced and even in homogenized liver, so that rapid removal of succinate is no guarantee of the integrity of the tissue. While it is interesting to find that the elements of the succinoxidase system are intact, even in severe shock, there is no assurance in this evidence that the enzyme complex is still in proper relation to the other enzyme systems of the liver. It is evidently in this relationship, as well as in the functional integrity of other liver enzymes, that an explanation of the depressed oxygen uptake of liver tissue from bled rats is to be sought.

The excellent correlation of the rise in blood amino nitrogen with the rate of oxygen uptake of the liver indicates that one consequence of shock is a failure of the liver to deal adequately with amino acids. At the moment there is no evidence to indicate whether this involves a failure of the liver to deaminate amino acids or whether the assimilation of amino acids may not also be affected. An accelerated protein breakdown in the peripheral tissues, in consequence of shock, has been described in a preceding paper (2). It is probable that the proteins of the liver are similarly affected by diminished blood flow and oxygen supply. In these circumstances the liver deaminases, if still intact, may be saturated with substrate of hepatic origin, and the normal assimilatory mechanisms, involving continued protein synthesis and breakdown, may fail for lack of the oxidative energy required to maintain these processes in proper equilibrium.

The different effects of glucose on the respiration of liver and of kidney, in shock and in anoxia, lend support to the interesting point that the order of resistance to damage of the tissues in these circumstances—liver < kidney < muscles—is the same as that of their ability to utilize glucose, both aerobically and anaerobically. The respiratory quotient of normal liver tissue is about 0.5, it does not use glucose readily as a substrate. This suggests that the low

rate of oxygen uptake of the liver in shock may be due to damage to enzyme systems responsible for the utilization of some primary substrate other than glucose

Profound effects of hemorrhagic shock on the metabolism of the liver may not be found in every circumstance or in every species Beecher and Craig (8) have carried out experiments similar to those reported here, using cats fasted for 24 hours and inducing shock by hemorrhage They did not observe any effects of their treatment on the oxygen uptake of liver or kidney slices from cats in which the blood pressure had been held below 70 mm of Hg for 13 to 30 hours Our own experiments on cats are as yet incomplete, but it appears that while the liver respiration is not seriously affected in hemorrhagic shock in the cat fasted for 24 hours, it is depressed to a marked degree if the cat is fasted for 48 hours before the experiment The cat, a large carnivore, and the rat, a small omnivore on a high carbohydrate diet, cannot be expected to be in similar nutritive states after a 24 hour fast Fasting may certainly affect the resistance of liver tissue to anoxia Beecher and Craig (9) have found that liver tissue from fed rats maintains a nearly normal rate of oxygen uptake after exposure to nitrogen *in vitro* for even 60 minutes, and we have been able to confirm this in a preliminary experiment

SUMMARY

1 With increasing severity of shock following hemorrhage in fasted rats there is an increasing depression in the rate of oxygen uptake, in oxygen, of liver slices from the bled animals The respiration of kidney tissue is only slightly depressed even in severe states of shock

2 The rates of oxygen uptake of liver tissue from bled rats are nicely correlated with the increases in blood amino nitrogen that follow severe hemorrhage

3 A supplement of coenzyme factors, in the form of a hot water extract of normal rat liver, increases the oxygen uptake of liver tissue from rats in mild shock, but is without effect on the respiration of liver slices from rats in moderate or severe shock

4 The ability of rat liver to oxidize succinate is not impaired even in severe shock, but the extra oxygen uptake does not improve the basal rate of respiration of the tissue

5 Effects on the rate of oxygen uptake of normal rat liver slices comparable to those seen after hemorrhage could be produced by exposing the tissue to an atmosphere of nitrogen for periods of 15 and 60 minutes This treatment had more marked effects on the respiration of kidney slices than are found after hemorrhage, but the kidney, unlike the liver, exhibited a marked degree of recovery in the presence of glucose

6 The significance of these findings is briefly discussed

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SATURDAY, APRIL 5, 1930

STATE SCIENTIFIC AID TO CRIMINAL JUSTICE

A government, for the protection of the people against crime, establishes an intricate legal machinery consisting of courts, prosecutors and police, and gives them statutory rules of thumb by which they may work. For the investigation of supposedly violent deaths the office of coroner or of medical examiner has been added. The office of coroner, as has been emphasized previously in these columns, functions poorly. The medical examiner system, for obvious reasons, does its work well. Although the necessary legal machinery and the laws are available, although the office of coroner or medical examiner is an agency that should utilize the facts of scientific medicine, our government falls short. The law defines the various gradations of crime with meticulous precision and lays down rules of legal procedure that must be followed with hair-splitting exactness but fails to avail itself of the aid which much more exact sciences might render.

The work of the coroner or of the medical examiner must of necessity be inadequate unless the office can avail itself of the laboratories of the medical sciences. The office deals with death, with the causes of death and with states of disease. Thus its work is not greatly different from that of the hospital. Yet the intelligent layman who would refuse to go to a hospital that did not maintain an adequate laboratory department permits the office of coroner or medical examiner to function without the aid of pathology, bacteriology, immunology, chemistry and toxicology, sciences that are of fundamental importance in establishing the cause and nature of any death.

The prosecutor, if he is to present a proper case, needs the results obtained by the application of these laboratory sciences. The court, if it is to be an instrumentality of justice, needs actual facts as much as do the prosecutor and the coroner or the medical examiner. The court, however, needs much more. It deals with living human beings, with those either justly or unjustly accused and with those who give evidence against the

accused. The determination of criminal responsibility by the ability to distinguish between right and wrong may have been a satisfactory legal rule of thumb in earlier days. But right and wrong are not absolute concepts to be as sharply opposed to each other as are black and white. The advances of psychology have shown that what may be right for one person may be wrong for another. The doctrine of absolute right and wrong as a measure of criminal responsibility belongs to the days when every mental aberration was treated by the strait-jacket or by confinement in a madhouse that was worse than a prison. In meting out true justice, courts need the information that can be given them by those who are actually expert in psychiatry and abnormal psychology. Such information should come from an unbiased and nonpartisan source, and not from partisan or bipartisan experts. The right of the defense or of the prosecution to hire as many partisan experts as either side may choose or be able to pay for need not be abrogated, but one would like to see the court itself in a position to turn for advice to a source that the court might feel is unbiased and animated only by a desire to seek the truth.

The most important link in the chain of criminal justice is the policeman on the beat. The government clothes him with authority, places a pistol in his belt and a mace in his hand, and expects him to prevent crime. As long as his inefficiency is not due to graft and dishonesty, he is not to be blamed if he fails to prevent crime or if he is unsuccessful in the apprehension of a criminal. He usually knows no more of the aspects of delinquency and criminality than do others in the walk of life from which he is chosen. Having been chosen, he is not given the specialized training that he should have. The policeman should have the fundamental training that would prevent him from clumsily and unwittingly destroying evidence that may be necessary for the detection of crime or for the conviction of the criminal. He should know, through his superiors in the department, that microscopy, chemistry, immunology, metallurgy, crystallography or ballistics may yield highly important information and he should know where such information may be obtained. Not only should photography and other methods of human identification be available, but the policeman on a beat should know enough of their use to know when they should be used.

The scientific aids, most of them medical in character, so necessary to the work of coroners, medical examiners, prosecutors, courts and police should be, as they are abroad, an essential part of the machinery of criminal justice, a function of the government. In urban centers the work of criminal justice may be so great as to require an organization whose activities are confined to the city. In general, however, the ideal solution would appear to be an organization, comparable to foreign institutes of legal medicine, supported and controlled by the individual states, that could serve the

various agencies of criminal justice throughout the state. That the state is capable of conducting work in the laboratory sciences is evident from the work of public health laboratories, of water surveys and of state toxicologists. That it can function creditably in matters relating to psychiatry and abnormal psychology is evident from the work of the Institute for Juvenile Research in Illinois, of the system of state psychiatric examination in Massachusetts, and of the state criminologist in those states that have such an official. In most states an entirely new and expensive organization would probably not be necessary. Correlation and coordination, under proper direction, of agencies already existing in many states might form the foundation of a useful organization. The police function is so preeminently a property of city government that the training of police would probably have to be done by the police department of the local city government. However, since some states have found it advisable to organize state police, a school for the instruction of state police might readily offer instruction also to city police detailed to it in small numbers for training. Some time, perhaps, newspapers will tell less of crime waves and more of concerted intelligent action to overcome crime and to decrease its incidence.

ANOTHER PORTER NARCOTIC BILL

On March 26, Representative Porter introduced a third narcotic bill, H. R. 11143, to create in the Treasury Department a bureau of narcotics and to remove existing limitations on the importation of coca leaves that do not contain cocaine or ecgonine and of certain salts, derivatives and preparations of coca leaves. The Committee on Ways and Means has already reported it and it is now before the House of Representatives for action. The bill as reported ignores the appeals made by the American Medical Association that cooperation be established between the federal narcotic service and the proper authorities of the several states, in efforts to suppress the abuse of narcotic drugs. It ignores, too, an appeal made by the Association that approved laboratories be authorized to import the rarer alkaloids and derivatives of opium and coca leaves that are not manufactured in the United States, for purposes of research under such limitations as the Federal Narcotics Control Board may impose. It takes care, however, of certain commercial interests that use, or profess to use, decocainized coca leaves in their businesses.

The federal narcotic service has repeatedly alleged that narcotic addiction is prevalent among physicians. It has claimed, too, that there is no method by which physicians addicted to the use of narcotic drugs can be prevented by law from obtaining them. The falsity of the latter statement has been pointed out to officers of the federal narcotic service, since the medical licensing boards of most of the states are empowered

to revoke the licenses of physicians who are addicted to the use of narcotic drugs. It is necessary only for the federal narcotic service to lay before the boards having that authority adequate evidence of narcotic addiction, in order to procure the suspension or revocation of the licenses of addicts. A rule promulgated by the Secretary of the Treasury, forbidding disclosure generally of the affairs of the Treasury Department, a rule that can be amended by the secretary at any time, is the only excuse that has ever been offered for the failure of the federal narcotic service to cooperate with the state medical boards. Until some adequate explanation of the failure of the federal narcotic service to procure an amendment of this rule by the secretary, so as to permit cooperation with the states, the only inference that can be drawn is that the service realizes that such evidence as it has will not bear scrutiny by disinterested fair-minded persons.

It was proposed to the Committee on Ways and Means and to Representative Porter, on behalf of the American Medical Association, that pending legislation looking toward the establishment of a Bureau of Narcotics require the proposed Commissioner of Narcotics to cooperate with the authorities of the several states in formulating adequate state laws and regulations to control narcotic drugs and in the prosecution of cases before state licensing boards and courts. The omission from the present bill of any authorization or requirement for such cooperation suggests that the plan proposed by another pending narcotic bill, H. R. 9054, of establishing federal control over the practice of medicine, dentistry, veterinary medicine and pharmacy in the several states, so far as relates to the professional use of narcotic drugs, has not been abandoned. Such a proposal should be resented as a proposed encroachment by the federal government on the rights of the states. Physicians, dentists, veterinarians and pharmacists, however, have more than an abstract patriotic relation to such a proposal. It means that their rights to practice their professions, so far as they require the use of narcotic drugs, will be dominated and controlled by federal field agents and by a federal bureau chief in Washington. If any provision is made whereby a physician may appeal to the courts to obtain his rights, it will be to the federal courts, not to the courts of his own state.

The fact that none of the bills recently introduced provide for the removal of the obstacles now in the way of research into the properties and uses of the rarer salts, derivatives and preparations of opium and coca leaves is of interest not only to the medical profession but also to the general public. Such obstacles tend to hinder the development of methods for the relief of pain and the treatment of disease. As the law now stands, no salt, derivative or preparation of opium or coca leaves can be imported into the United States. When there is a sufficient commercial demand for any of these to justify its manufacture in the United States,

the law works no harm, for it allows the importation of as much crude opium and coca leaves as are necessary for that purpose. On the other hand, when there is no commercial demand for such a salt, derivative or preparation sufficient to justify its manufacture in the United States, research workers in the United States are unable to study it with a view to determining its properties and uses. Representative Porter was requested by letter, May 3, 1929, to incorporate in any amendment of the Narcotic Drugs Import and Export Act that he might prepare a provision whereby laboratories desiring to investigate the property of these rarer salts, derivatives and preparations, and to obtain papaverine and similar drugs, might import them under proper regulations. The omission from the two bills previously introduced by Representative Porter of any provision to meet the situation was attributed to the fact that they did not seek to change the scope of the Narcotic Drugs Import and Export Act. The present bill, however, proposes to limit the scope of that act in other respects, and the amendment that was proposed to provide for scientific research therefore was and is germane. The present bill proposes to remove restrictions on the importation of coca leaves and to authorize the importation, without limit, of coca leaves that do not contain cocaine or ecgonine, or any salt, derivative or preparation from which cocaine may be made, and the importation of any salt, derivative or preparation of coca leaves which does not contain cocaine or ecgonine or any ingredient from which cocaine or ecgonine may be made. Why such a concession should be made and the legitimate needs of the medical profession ignored is not explainable by anything in the bill.

The present bill is objectionable in that it proposes to substitute a single federal officer, ranking as a commissioner, in place of the federal Narcotics Control Board, made up of three cabinet officers. Even, however, if a misguided commissioner of narcotics should arbitrarily limit the importation of opium and coca leaves so much as to create a scarcity of their medicinal derivatives, it is hardly possible that manufacturing pharmacists will ever be unable to furnish a reasonable supply of such drugs at prices within the reach of average patients. The problem of such limitation is primarily a problem for the people, not for the medical profession, for it is the people who will suffer in event of a scarcity. On the other hand, federal cooperation with the states in the enforcement of federal and state laws, instead of the assumption by the federal government of autocratic control of the professional use of narcotic drugs within the states, is of primary interest to the medical profession. So also to a large extent is the matter of the importation of the rarer forms of narcotic drugs for purposes of research. Unless the pending bill is amended so as to insure federal cooperation with the states and to permit the importation of the rarer forms of narcotic drugs for purposes of research, under proper restrictions, the

bill must be considered objectionable and should be opposed. Protests should be sent promptly to every member of the House of Representatives by physicians, individually and through their organizations.

The bill here discussed, H. R. 11143, pending before the Committee on Ways and Means, should not be confused with another of the narcotic bills, H. R. 9054, introduced by Representative Porter, January 23, and pending before the Committee on Foreign Affairs. The latter bill proposes to vest in the Commissioner of Prohibition autocratic powers over the professional use of narcotic drugs by physicians, dentists, veterinarians and pharmacists, and to that extent it proposes to limit the powers of the states with respect to the regulation of the practice of medicine and the other professions named. If the bill here under consideration should be enacted, the autocratic powers that it is proposed in the other bill to vest in the Commissioner of Prohibition would be transferred to the Commissioner of Narcotics. Representative Porter, however, has agreed not to take up the consideration of the bill enlarging the powers of the Commissioner of Prohibition until after it has been considered by a subcommittee of the Committee on Foreign Affairs, in conference with committees appointed by the American Medical Association and by pharmacists. The Executive Committee of the Board of Trustees of the American Medical Association, March 28, appointed a committee to represent the American Medical Association in the matter.¹

Current Comment

GRAPE JUICE AND ACIDITY OF THE URINE

The body is essentially an acid-producing organism. One of the most important of the energy-yielding biochemical reactions is the oxidation of the carbon contained in food materials to carbonic acid. The metabolism of the sulphur and phosphorus in proteins likewise yields end-products that are acid. In spite of this recognized tendency to the production of acids, the slightly alkaline reaction of the blood and body fluids is maintained with great efficiency. Not only do the buffer systems in blood and tissue fluids maintain an almost constant reaction, but, in addition, the lungs and kidneys are active in removing acids. Obviously, then, there is a constant demand for base in the body, the food constitutes the ultimate source of the required alkali. Vegetables and fruits yield an alkaline ash in the laboratory, and a similar behavior has been demonstrated in many instances in the body. Indeed, it has been shown that oranges, apples, pineapples and tomatoes, fruits with juice of more or less pronounced

¹ The committee consists of Dr. Robert L. Anderson, Pittsburgh; Dr. S. Dana Hubbard, New York; Dr. J. R. Neal, Springfield, Ill.; Dr. Torald Sollmann, Cleveland; Dr. J. H. J. Upham, Columbus, Ohio; and the following ex officio members: Dr. Edward B. Heckel, chairman, Board of Trustees of the American Medical Association, Pittsburgh; Dr. William Gerry Morgan, President Elect, American Medical Association, Washington, D. C.; and Dr. William C. Woodward, legislative counsel, American Medical Association, Chicago.

acidity, yield alkali in the course of metabolism sufficient to change the reaction of the urine. That this type of action is not characteristic of all fruit juices, however, has recently been shown again by Pickens and Hetler,¹ who examined, among other things, the acidity of the urine in human subjects who had drunk large quantities of grape juice. When, under carefully controlled experimental conditions, as much as a quart of grape juice daily was ingested, neither the titratable acidity nor the hydrogen ion concentration of the urine was significantly altered. This is not the only example of the failure to decrease the acidity of the urine by a fruit with an alkaline ash. Blatherwick² has shown that the ingestion of prunes, plums and cranberries results in an actual increase of acidity of the urine, owing, probably, to the content of benzoic or other similar acids in these particular fruits. One puzzling aspect of the behavior of the unfermented, sweetened grape juice used in these studies is the fact that raisins are known to decrease the acidity of the urine. In view of the growing tendency to adopt dietotherapeutic alkalization by means of fruits and fruit juices, it is well to point out that not all fruits are effective in this regard.

THE KIDNEY-SHAPED FEMALE PELVIS

Uncivilized and primitive peoples usually give birth to their children easily because the pelvis is round. With civilization came the kidney-shaped pelvis, delivery by forceps, and cesarean section. In some countries of the orient, the primitive and the civilized live side by side, thus in China, according to Kathleen Vaughan, cesarean section is a frequent operation but is confined to the superior class of Chinese, who live much indoors and bind their feet so that exercise is impossible. Outside Bombay, the women of the weaver caste engaged in the numerous outdoor occupations of village life have large families with little trouble in parturition. The same women brought into the city of Bombay and living a sedentary life in the dark streets have such great difficulty in childbirth that the caste is maintained only by the constant influx of country people. Dr. Vaughan³ attributes the kidney-shaped pelvis not only to the softening of the bone from lack of sunlight and of vitamin D but also to the lack of exercise of the sacro-iliac joint. It has already been shown that ankylosis of these joints results in atrophy of the sacrum and of both ilia unless the ankylosis is unilateral, in which case the pelvis fails to develop on the corresponding side. In examining pelves at the College of Surgeons, Dr. Vaughan observed that the auricular surface of the sacrum in apposition with the first three sacral vertebrae is much more extensive in native races, so that there is a larger surface covered with cartilage to influence bone growth. The joint, comprised by a projection from the ilium into a depression of the second sacral vertebra, on which the sacrum

moves backward and forward, is always well developed in circular pelves and is accompanied by a large auricular surface. She suggests that, if the mobility of this joint were maintained by Westerners as it is by the uncivilized peoples of the East and in Africa, the pelvic deformities leading to difficult labor might be eliminated.

FACTORS IN PUERPERAL SEPSIS

In the attempt to make some inroad on the obstinately high morbidity and mortality from puerperal sepsis, emphasis has been laid on preserving the asepsis of the genital tract during labor. Many obstetricians have abandoned the use of vaginal examinations even with the gloved finger. La Vake,¹ who holds that in 95 per cent of cases that will terminate spontaneously vaginal examination is unnecessary, has used rectal examination as a routine in these cases since 1913. His experience accords with that of many others who claim that this procedure reduces morbidity during the puerperium. Among those who have not found this advantage in the substitution of the rectal method is Reis,² whose study comprises 609 patients examined by vagina, 271 by rectum, and 106 delivered without examination. Pelvic infections were rather more frequent among those rectally examined than among those examined by vagina. There was, however, a distinctly lower morbidity among the women who received no examination at all. Two possible interpretations suggest themselves to account for this result. Perhaps the 106 in whom labor was left entirely to nature were selected cases in which labor was particularly easy. The rectal as well as the vaginal examination, however, by manipulation in the neighborhood of the cervix, is liable to convey bacteria already present in the vagina to the cervical canal. The great care that is taken at the time of parturition in preserving the aseptic integrity of the reproductive passage is in rather marked contrast to the indifference usually displayed as to the safeguarding of this route in the days immediately preceding labor. The careful obstetrician can hardly afford to overlook the possibility of such contamination. Even supposing that the reproductive canal is aseptic at the onset of labor and is not infected during the stages of labor, the puerperium is still not secure. Armstrong³ has described three epidemics of puerperal sepsis at St. Bartholomew's Hospital in which he considers evidence as convincing that they resulted from "air-borne" infection. Armstrong suggests the exclusion from maternity wards of all possible carriers of streptococci as well as all those who may be subject to streptococcal infection of any kind, and, as an additional precaution, the use of gauze masks. Trauma occurring during parturition remains a factor of high importance. Among 2,000 deliveries in the maternity district of the hospital, puerperal morbidity was found to be 10 per cent higher after instrumental than after spontaneous delivery.

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(Continued from page 1000)

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

FEBRUARY 17—AFTERNOON

IMPORTANCE OF PATHOLOGY IN MEDICINE

Opportunities for the Study of Morbid Anatomy in the United States and Canada

DR LOUIS B. WILSON, Rochester, Minn. The Council on Medical Education, in its attempt to encourage hospitals to increase the number and improve the quality of their autopsies, is constantly meeting with the complaint from hospital authorities that there are not nearly enough competent pathologists available to do the required work. In conversations with heads of departments of pathology in medical schools, one gets the impression that there are relatively few young medical graduates in training as pathologists in the United States, though some think that there is an increasing percentage of graduate physicians who are spending from three months to a year in pathology as a preparation for the practice of clinical specialties.

In order to determine if possible the facts concerning these two groups, a questionnaire was sent to the heads of pathologic departments in medical schools and to the chief pathologists in a few large hospitals not connected with medical schools. Replies were received from fifty-five pathologists. The total number of autopsies performed by them during 1929 was 20,952. Of these, 17,608 were done by thirty-five men, who each did 200 or more.

Thirty-five European pathologists performed about twice as many autopsies in the same period as the highest thirty-five in the American group reporting to the questionnaire. With at least thirty-five pathologic departments in America each performing more than 200 autopsies a year, if the average were 500 each there would seem to be enough material for the training of a considerable number of physicians in autopsy practice. Almost all of the pathologists reported that the autopsies performed by them were open to graduate students to act as assistants. It is difficult to understand why any pathologist except perhaps in coroner's cases should exclude from among his assistants all those who were not fully trained in autopsy technique.

A second factor in the problem is the extent to which the opportunities for assisting at the autopsy are taken up in the teaching of undergraduates and of interns on general hospital services. It is difficult to interpret what the reporting pathologists meant in every instance, but so far as can be determined the status at present is as follows. The total number of graduate students including interns and residents, reported by the fifty-five pathologists was 171. Of the fifty-five schools reporting, fourteen apparently had no graduate students of any sort. In the other services there were eighty-three interns, ten resident pathologists, ten members of the junior pathologic staff and sixty-eight graduate students of all other varieties. In addition to the 171 graduate students in pathology of all varieties now listed in the fifty-five hospitals replying to the questionnaire, there would appear to be opportunity, according to the statements of the pathologists concerned for the further training of seventy-six more graduate physicians in pathology than are now enrolled.

A third factor is the inadequate or 'lopsided' organization of many pathologic departments. With limited budgets and laboratory space, a few promising young graduates are engaged to teach and conduct research. Once such a graduate is a member of the teaching staff, whether he is designated assistant, instructor, or what not, his duties are apt to be much more largely teaching than learning. And this is at a time

when he should be devoting himself to the study of pathology in all of its bearings, much more than to teaching undergraduates. Just how much time may be necessary for a graduate physician, who has had the start of at least one year of general hospital internship and who is working to best advantage in an adequate pathologic service supervised by a competent and inspiring pathologist, to become capable of heading or at least taking second place in the pathologic laboratories of a medical school or of a large hospital is impossible to say. Much depends on individual aptitude. My experience, however, would seem to indicate that three years is the average period. Training and experience in teaching on the part of the graduate student of pathology should be considered an adjunct of his training rather than the principal part of it.

A fourth factor is the lack of proper publicity concerning the opportunities available in the United States. Many young physicians have the mistaken notion that Europe is the only place where opportunities for assisting in autopsies may be obtained. If the autopsy services now in being in America were organized to the best advantage, it would be found that there is ample service not only for the adequate teaching of undergraduates and the training of general interns and residents in the specialties but also for the training of pathologists. It is suggested that pathologists heading university departments who have adequate unutilized facilities for the training of even one more man for a period of two or more years should state this fact through the ordinary channels of publicity of the university. It would appear desirable to include in this publicity a bulletin board announcement. Such an announcement should state clearly the facilities available, the entrance requirements, the minimum period of residence and the financial arrangements.

Educational Influence of Pathology on House Officers in a Teaching Hospital

DR HOWARD T. KARSNER, Cleveland. The hospital can well be thought of as a graduate school and the house officers 'so dealt with that the mere acquisition of knowledge shall not crush originality of intellectual endeavor.' Indeed all encouragement should be given the exercise of a sane imagination. Each house officer in a hospital has a mental equipment which is inborn and which has been influenced by general and technical education. The product of these is the material which will be subjected to further education by the hospital staff. The most satisfactory result is to be obtained by a sympathetic understanding of the inherent qualities of these minds and of the directional effects of the educational forces to which they have been subjected. The student in his medical school is in a sheltered microcosm, with his time plotted as in a railroad schedule and his studies arranged and guided for him by his instructors. Even in the most liberal curriculums he has but little freedom of choice. One of the functions of his school is to save him time and effort in the selection and assimilation of those facts and well established hypotheses prepared by his predecessors. His predilections and interests may emphasize certain fields of study to his own well being but he must cover his field with philosophic breadth and so far as his work in pathology is concerned must harmonize it with the systematized whole.

His cosmos in the hospital is broadened as his more intimate contacts with the staff, with his fellows and with the patients necessitate. His intellectual efforts acquire a greater freedom in accord with his capabilities. Pathology occupies a larger share of his thought than is ordinarily true when he goes into practice. What pathology brings to him in the hospital depends on the professional pathologist, the group of interested clinicians and himself.

The professional pathologist in the hospital therefore has a heavy responsibility for the welfare of the house officers, which only a genuine enthusiasm for the place of pathology in medicine will enable him to meet. His end can be gained by humility and enthusiasm, humility in the face of an ever broadening field of problems and enthusiasm in the effort to solve them. The hospital house officer will profit from a study of pathology in the institution in accord with his own interest, that of his chiefs, the material which both provide for study and the intelligence and enthusiasm of the pathologists. Occa-

the results of the analyses, his qualifications are thus far non-medical. If, in addition, clinicians may assume responsibility for the medical connections and applications of the work without themselves being proficient in it, clinical pathology is nonessential as a medical specialty. The field of laboratory medicine has become a large one, involving examinations of a highly complex order and practices of a high character. It will become still larger and the practices and procedures more complex and difficult. Some clinicians are and will be thoroughly conversant with the phases of laboratory examinations although they might not be able to carry out the examinations themselves. Such physicians might safely entrust the actual examinations to trained technicians, provided they may be assured of the technicians' proficiency and trustworthiness. The great majority of practicing physicians are entirely incapable of utilizing the medical laboratory on their own responsibility.

The clinical pathologist is in constant touch with the progress of medicine in general and of laboratory medicine in particular. He qualifies as a medical consultant. But he should not aspire to encroach on the clinical field as some would apparently like to do. Even clinical pathologists who enter other fields of practice soon lose their proficiency in their former work.

Such an understanding of this specialist and of the value of his work to medicine brings into reproach all practices wherein lay technicians are elevated to this responsibility or whereby medical laboratory work is lowered to the plane of uncontrolled laboratory technique. It outlaws the commercial laboratory in medicine. Such an understanding classifies clinical pathology as an essential medical service which can exist only through reasonable and proper economic support. Obviously the medical specialist concerned cannot work on the same economical basis as the lay technician. There has been much said of the additional cost of medical care on account of the laboratory expense. Laboratory medicine is probably the medical service of lowest actual and proportionate cost to the sick. Apparently its cost cannot be lowered and the specialty retained. Any suggestion of cutting the cost of medical care at this point should be critically analyzed, particularly for "smoke screens." Necessary examinations by a proper expert properly paid may not be as expensive as unnecessary or improper examinations by cheaper means. Many people are now paying for laboratory work which they do not get or do not need or which it would be better that they should not have, but it would indeed be an event to find an instance of an exorbitant charge for an examination done by worthy technicians.

As long as there are sick people there will be a need of laboratory medicine. That need will be properly and fully cared for only by the medical specialist. When patients are well hospitalized there will usually be no field for a private clinical laboratory. When their number is sufficient within a convenient radius there should be an opportunity for a clinical pathologist. The responsibility of the profession at large in the matter is also an adherence to the principles involved, and it is and should continue to be the business of organized medicine to hold these clearly before the profession.

DISCUSSION ON PAPERS OF DR. WILSON, KARSNER, BASS AND LYNCH

DR. ERWIN D. FUNK, Reading, Pa. If we turn back the pages of medical history fifty years, we find that the physician relied largely on his own good judgment as to what he could observe of the physical condition of his patient. Today much more is expected of that judgment because of the infinitely broader foundation on which it rests. That foundation consists not only of pathology but also of anatomy, physiology and biochemistry. We may call these the great triad on which the physician can build his superstructure. The small hospital, not connected with a college and far from a large medical center, can become an excellent source for postgraduate study for medical house officers and staff physicians. The pathologic department is the hub about which all teaching may revolve. The guiding spirit in this movement of pathologic research and clinical teaching is undoubtedly the clinical pathologist who not only is well versed in morbid anatomy but combines that rare ability to evaluate the clinical and functional importance of his observations. He must encourage his staff and house

officers to follow as many cases as possible to the necropsy table. It is the duty of the pathologist to let no clinical diagnosis in the event of death go unchallenged until he has exhausted every honorable means of securing a necropsy. In our hospital the clinical pathologist talks to the physicians, nurses and interns on how to "sell" necropsies. If such a procedure is productive and successful, there is always sufficient pathologic material present for a study of the morbid anatomy and its relation to clinical medicine. Our greatest difficulty has been to have the physician always present at the time of necropsy. This has been largely overcome by having private clinicopathologic conferences with the physician at his convenience. One way in which hospitals can raise their standard of practice is through pathology. It also encourages the physician to read more, and thereby he becomes a better teacher for the house officers. The more assiduously the physician investigates his failures, the more he will develop that great essential necessary for the practice of medicine called imagination. Of what value is observation or accumulation of facts if one has not the imagination to appraise them?

DR. H. E. ROBERTSON, Rochester, Minn. Twenty-five years ago, when I went into the specialty of pathologic anatomy, I had to face the prejudice that existed in the minds of most medical men against any one entering one of the basic sciences. Today pathology and pathologic anatomy occupy a tremendously important place in medical practice and medical teaching. Why? Because the whole medical world has its eyes directed toward the pathologist who is making postmortem examination and who will tell them the truth about the case. What constitutes proper training for such an individual? How long does it take to make a pathologic anatomist? My answer is that he is never "made." All we can do is to make him a going concern or give him the chance to become a going concern, so that he travels somewhat well on his own steam, but even then, if he has not the spirit born in him, he will soon slow down, and he does not become a real specialist in his field any more than any other specialist does. It takes about two or three years to make a pathologic anatomist—an individual who has a little steam of his own to carry himself along. The field of pathologic anatomy was never more of an active field, never richer in possibilities, than it is today. What we need to do as pathologists, as heads of hospitals, as heads of medical schools, is to see to it that the mantles of those who are in charge of the field shall fall on the individuals who can carry on the work. In practically every hospital in this country there are enough facilities, and in many the head pathologist possesses enough initiative and inspiration to transmit interest to some other individual and make him a going concern. Dr. Wilson's survey shows clearly that our facilities are wonderful in this country.

DR. L. H. PRINCE, Hines, Ill. The United States Veterans Bureau found it impossible to get a sufficient number of pathologists to supply fifty or so hospitals. It therefore became incumbent on the bureau to train some of the members of the medical staff. At the present time I have a class consisting of six members. It must be remembered that in our institutions there are certain administrative difficulties over which we have no control and which are insurmountable. We must interpret every one of our activities in terms of dollars and cents. The maintenance cost of each hospital must be reduced to the day of relief standard. The training of individuals in pathology therefore became an acute problem, and in some of our institutions in outlying places, it was utterly impossible to maintain a pathologist and a roentgenologist at the same station, because there was not enough work for either one. It was necessary to combine the two activities. Therefore, in addition to being a competent pathologist, a man so stationed must also be an expert in roentgenology. The problem is not an easy one to handle. We avoid most carefully offending the clinician. I do not wish to convey the idea that the bureau is not generous in its supplies and material. We can get practically everything we request and within a reasonable length of time. Everything that is necessary to conduct the work in the interest of the beneficiaries of the Veterans Bureau is handed out without any objection. There seems to

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION, PUBLIC HEALTH, ETC.)

CALIFORNIA

Hospital News—The new \$1,650,000 Cedars of Lebanon Hospital will be dedicated, April 27, it has 275 beds, and adjoining is a nurses' home with eighty rooms and an auditorium seating 300. About one third of the hospital beds will be devoted to those who cannot pay for medical care.

Personal—Dr. Sven R. Lokrantz, medical director, Los Angeles city schools, recently was decorated by the King of Sweden for 'his health work for the children of California and in a lesser degree for the children of Sweden.'—An honorary doctorate was conferred by the Medical Faculty of the University of Freiburg, March 11, on Dr. Herbert M. Evans, professor of anatomy, University of California Medical School, Berkeley, in recognition 'of his conspicuous anatomical and biological discoveries, especially in the sphere of vitamin research, both of which are scientific and of world interest.'

Society News—At the annual meeting of the California Tuberculosis Association in Merced, April 7-8, Dr. Joseph W. Mountin, U. S. Public Health Service, will speak on "Tendencies in Public Health Organization and Their Relation to the Tuberculosis Program," Dr. Henry Cheslev Bush, Livermore, on "Parenchymatous Lesions in Childhood," Dr. Robert A. Peers, Colfax, on "Blood Sedimentation in Tuberculosis," and Drs. Philip H. Pierson, and William R. P. Clark, San Francisco, on "Healing in Tuberculosis."—The Pacific Physiotherapy Association was addressed, March 26, by Dr. John Severy Hubben, Pasadena, on "The Visible Spectrum and Infra-Red Frequencies."—The Los Angeles County Medical Association and the Physicians' and Surgeons' Fellowship Club were addressed at a joint meeting, March 20, by Dr. Lewis Gunther on "Root Pain of Osteo-Arthritic Origin as a Confusing Factor in Diagnosis" illustrated, Dr. Howard L. Updegraff, "Problem of Total Rhinoplasty," illustrated, Dr. William H. Daniel, "Proctology, Ambulant and Operative," and Dr. Conrad J. Baumgartner on the diagnosis and treatment of goiter.—The Yuba Sutter Counties Medical Society was addressed at Marysville, recently, by Dr. Albert H. Rowe, Oakland, on "Food Allergy."

DISTRICT OF COLUMBIA

Society News—The Board of Trade of Washington is making an inquiry into the use of roentgen ray films in Washington hospitals and by local physicians to determine the quality and manner of storage of roentgen ray films.

Psittacosis Has Attacked Eleven Laboratory Workers—In view of the fact that eleven employees of the Hygienic Laboratory in Washington have contracted psittacosis during the investigation at that institution, the work will be transferred to one of the government quarantine stations. While no definite selection has been made of the station, one of the following is expected to be chosen: Craney Island, near Norfolk, Va., Reedy Island, in the Delaware River, Swineburne Island, at New York.

Lieut.-Col. Garrison Retires—Goes to Johns Hopkins—Lieut.-Col. Fielding H. Garrison will assume the duties of librarian of the Welch Medical Library of the Johns Hopkins Medical School May 1, when he will retire from the U. S. Army. The library represents a consolidation of three great collections of books—of the Johns Hopkins Hospital, of the School of Hygiene and Public Health, and of the School of Medicine. It has a capacity of 500,000 volumes and was named in honor of Dr. William H. Welch, who has taught at Johns Hopkins for about forty-five years. Dr. Garrison was assistant librarian in the surgeon general's office, Washington, D. C., from 1889 to 1922, and is the author of the well known History of Medicine.

Washington Stands Alone—No Sanatorium for Children—A committee under the auspices of the Washington Tuberculosis Association has been appointed to call the attention of the public to the need for a sanatorium for tuberculous children in the District. Surg. Gen. Hugh S. Cumming, U. S. Public Health Service, says that Washington is the only large city in the world which is not provided with a sanatorium or hospital to care for tuberculous children. The Children's Tuberculosis Clinic was organized last April by the association

in cooperation with the health department, and since that time there have been 2,841 visits of child patients, 951 patients admitted and 178 children found to be infected with tuberculosis in this period also at least five cases of juvenile tuberculosis have changed to the adult type of the disease.

FLORIDA

Dr. Williams Sentenced—Dr. Horace J. Williams, Tampa, who it is reported pleaded guilty in February before the federal court of violating the Harrison Narcotic Act, was sentenced to five years in the federal prison or given the option of leaving the United States. He is reported to be planning to leave the country.

ILLINOIS

Personal—Dr. Joseph De Silva was elected president and Dr. Stuart W. Adler secretary of the Rock Island Physicians Club, Rock Island, March 6.—Dr. Floyd E. Fielding has been appointed health director of Bloomington, succeeding Dr. Henry H. Bishop.

Chicago

The Book Racket—A man giving his name as H. R. Carter, who represents himself as a member of the American Legion, has been soliciting orders for a list of seven books on 'Official Source Records,' stating that the proceeds are to be used for disabled war veterans. On investigation it was found that the legion is not receiving the benefits and that this is a high powered book racket which should not be encouraged. The agent endeavors to collect the cash price, \$98. He gives no receipt and leaves no literature for identification.

Society News—Dr. Russell L. Cecil, assistant professor of clinical medicine, Cornell University Medical College, New York, will address the Chicago Medical Society, April 16, on "Etiology and Treatment of Chronic Arthritis."—The Chicago Urological Society was addressed, March 27, by Dr. Samuel J. Sullivan on "Gonorrheal Keratosis," by Dr. Robert E. Cumming, Detroit, "Urography, The Development of a New Method with Physiologic Data," and by Drs. Harry B. Culver and Walter F. Hoepfner, "Management of a Case of Bilharziasis."—"Hearing Examination and Conservation" was the title of an address by Dr. Austin A. Hayden before a joint meeting of the Chicago Laryngological and Otological Society and the Chicago Medical Society, March 26. Dr. George W. Boot spoke on "Cancer of the Larynx."—The Chicago Laryngological and Otological Society will be addressed, April 7, by Dr. William Bloom on "Anatomy and Histology of Reticulo-Endothelial System," illustrated, Dr. Paul R. Cannon on "Reticulo-Endothelial System as a Defensive Mechanism" and Dr. Samuel M. Feinberg on "Nasal Allergy as Related to Hyperesthetic Rhinitis and Hay-Fever."—The Chicago Society of Industrial Medicine and Surgery was addressed, April 2, by Dr. Volney S. Cheney on "Aggravation of Pre-existing Disease by Trauma," and by Dr. Ramon Castroviejo on "Slit Lamp in the Diagnosis of Interocular Foreign Bodies."—Among others, Dr. John L. Yates, Milwaukee, addressed the Chicago Surgical Society, April 4, on "Making and Closing of Laparotomy Wounds."—Dr. Francis R. Pickard, Philadelphia gave an illustrated lecture on "William and John Hunter a Study in Contrasts" before a joint meeting of the Institute of Medicine and the Society of Medical History of Chicago, March 28.

INDIANA

Society News—Dr. Stuart Pritchard, Battle Creek, Mich., will address a joint meeting of the Indianapolis Medical Society and the Marion County Tuberculosis Association, April 8, on "Significance of Cough." The medical society will be addressed, April 22, by Dr. Russell R. Hippensteel on the malnourished school child, and by Dr. Charles D. Humes on "Parkinson's Residues of Encephalitis," illustrated, April 29, the speaker will be Dr. Ernest Sachs, St. Louis, on "Early Diagnosis of Brain Tumors."

KENTUCKY

Federal Narcotic Farm to Be in Kentucky—The treasury department has selected a thousand acre site, located 4 miles from Lexington, for the first of the two narcotic farms authorized by Congress. Prisoners in federal penitentiaries who are drug addicts will be transferred to the farm for treatment and rehabilitation which cannot be adequately carried out under present conditions in the penitentiaries.

Appointments to State Board—The following members of the State Board of Health of Kentucky were appointed by the governor and confirmed by the Senate, March 20: Dr. E. Murphy Howard, Jr., Harlan, president; Dr. George S. Coon, Louisville; Dr. Benjamin B. Keys, Murray; Carl J.

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THE EOSINOPHILIC RESPIRATORY SYNDROME

ERNEST SOYSA, O B E , M B (Lond), M R C P (Ed)

Major, Ceylon Army Medical Corps, Consultant Physician,
Royal Air Force, Ceylon

BRONCHIAL ASTHMA accounted for a considerable amount of morbidity among Ceylonese, Indian and African troops stationed in Ceylon during the last war. In many of these cases we found eosinophilic leucocytosis and radiological changes, and it was possible to return all such patients as fit for duty after arsenical treatment, with an appreciable reduction in invalidism due to respiratory disability in the services (Soyso and Jayawardena, 1945, Soysa, 1949).

Though observed nearly three decades ago by de Langen and Djamil (1923), this eosinophilic respiratory syndrome was not fully described until Fridodt-Moller and Barton (1940) analysed their investigations of 175 cases. What is known or has been suspected about the natural history of this symptom-complex is implied in its various synonymous designations—eosinophilic bronchitis, pseudo-tuberculosis, lecithinophile eosinophilia, intrinsic asthma, tropical eosinophilia, benign eosinophile leukæmia, eosinophilic lung, pulmonary acariasis, hyper-eosinophilic asthma, tropical pulmonary eosinophilia, etc—but none of these titles adequately fulfils the requirements of a precise definition.

NATURE OF THE SYNDROME

Clinical Features—The condition runs a benign course, varying from indefinite ill health with occasional mild cough to the typical symptom-complex which presents three stages.

The prodromal stage is insidious in onset, with malaise and anorexia progressing gradually to a febrile coryza and an intermittent dry cough.

The bronchitic stage is characterised by spasmodic, dry nocturnal cough sometimes associated with irregular, low fever, occasional enlargement of the spleen and lymph glands, and asthenia induced by disturbance of sleep by the hacking cough and malnutrition due to anorexia.

The asthmatic stage usually succeeds the bronchitic phase, but sometimes replaces one or both of the preceding stages, and occasionally appears with an acute, explosive onset, particularly in children and adolescents. Symptoms vary from occasional, mild, nocturnal expiratory dyspnoea to distressing status asthmaticus. Deterioration

A paper read at the Annual General Meeting of the Clinical Section of the Royal Society of Medicine on 8th June 1951.

of health often follows the lassitude and exhaustion caused by increasing loss of sleep and weight. Pyrexial and splenic signs are much less evident during this phase.

The nature, incidence and duration of these clinical features are subject to considerable variation. Most patients who have been affected for over a year find that relapses tend to diminish in frequency and intensity with longer intermissions. In this chronic stage some patients become debilitated by progressive diminution of respiratory efficiency and impairment of general health; others become adapted to occasional mild pulmonary discomfort without suffering much constitutional disturbance.

Radiological Features—Even more variable than the symptomatology of this syndrome are its radiological features. Various gradations may occur between normal pulmonary radiolucency and the pathognomonic eosinophilic lung patterns—

- (a) Gross increase in the bronchovascular markings, giving rise, at first to widespread linear striations, and later producing a generalised obscuration of the lung fields commonly referred to as the “ground glass haze” or “snowstorm picture” (Fig 1)
- (b) Disseminated nodal opacities producing a mottling of the lung fields that is similar in many respects to the appearance of disseminated tuberculous lesions and has, therefore, been loosely labelled as the “miliary picture” (Fig 2)

Hæmatological Features—The blood picture of this syndrome is its most remarkable and constant feature, namely, a massive eosinophilic leucocytosis which is not associated with immaturity or other abnormality of the eosinophils or with any other significant hæmatological disturbance. The eosinophilia may be evident even when the clinical and radiological features have not yet developed, are in natural abeyance, or have been therapeutically abolished.

The extreme leucocytosis, which often exceeds 75,000 cells per c mm, is determined by an intense eosinophilic reaction which may account for as much as 90 per cent of the white corpuscles. The absolute concentration of eosinophils in the blood usually ranges between 1000 and 50,000 cells per c mm. The highest recorded figure is 2,100,000 eosinophils per c mm (Wilson, 1950). The eosinophilia may exhibit spontaneous, inexplicable fluctuations, sometimes dropping low for a few days and then returning rapidly to its previous level (Fig 3).

Pathological Features—The benign nature of this syndrome limits opportunity for the study of its morbid anatomy. Necropsy findings in a few cases which had terminated fatally from other causes have been reported by Meyenburg (1942) and Viswanathan (1947). The scanty data so far available suggest the inference



FIG 1—Eosinophilic Respiratory Syndrome Radiological appearances in the ‘ground glass haze’ obscuration of the lung fields

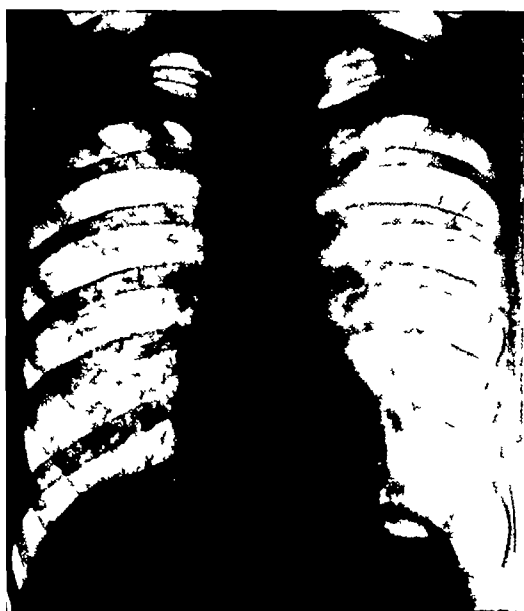


FIG 2—Eosinophilic Respiratory Syndrome Radiological appearances in the “miliary type” of disseminated mottling of the lung fields

that the pulmonary changes comprise diffuse bronchiolitis and peribronchial cellular infiltrations causing scattered, focal pneumonic lesions

Therapeutic Features—Since Weingarten (1943) reported his chance cure of this syndrome with arsphenamine, oral and intravenous medication with organic arsenicals have become so well established as almost to constitute a therapeutic test

After adequate trial of various schemes of treatment, both oral and parenteral, I have reached the conclusion that effective control of the condition can be established in the majority of cases with a ten-day

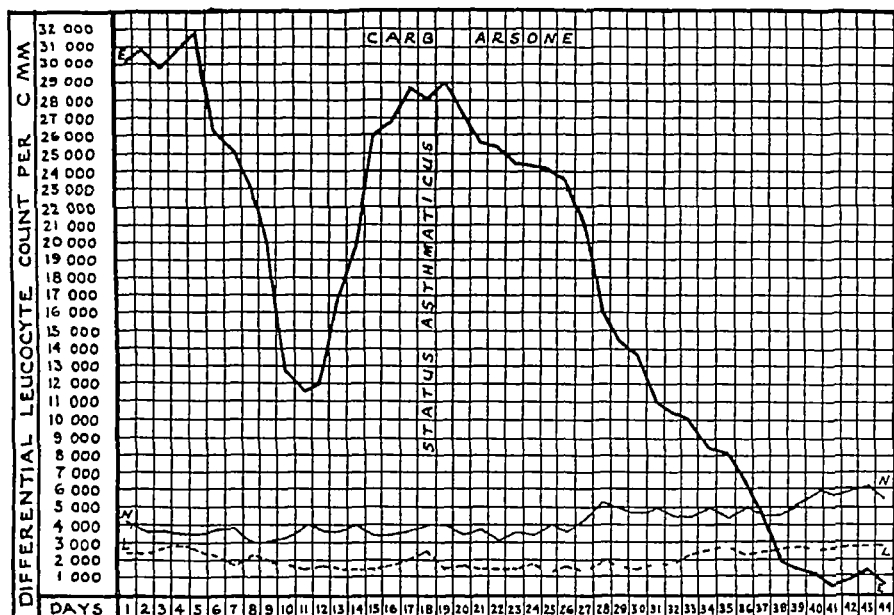


FIG 3—Eosinophilic Respiratory Syndrome Differential leucocyte chart showing eosinophilic reaction (E) before, during and after ten days' arsenical therapy, with no associated disturbance of neutrophils (N) and lymphocytes (L)

course of oral therapy divided into two stages of four and six days separated by a two-day interval. Good results have been achieved with a dosage of one 0.25 gm tablet of carbarsone given twice daily after meals, involving a total ingestion of 1.44 gm of arsenic. A Herxheimer reaction frequently occurs between the third and fifth days of treatment, with clinical exacerbation, sometimes producing status asthmaticus, and an eosinophilic increase. This almost invariably presages a rapidly effective therapeutic response.

Gastrointestinal, hepatic, encephalitic and other complications of arsenical medication have been conspicuously absent in my personal experience, this might, possibly, be attributable to adherence to a restricted schedule of administration of arsenic and strict enforcement of rest during treatment.

ORIGIN OF THE SYNDROME

What remains unknown about the origin of this syndrome may be even more significant than what is known about its nature. A few suggestive observations gathered from ætiological study may be correlated with clues to the pathogenesis detected by laboratory search.

Age, sex and race have no ætiological significance other than might be incidental to environment. The possible significance of environment was suggested by the observation that 80 out of 100 cases studied in Ceylon (Soyso, 1949) showed evidence of exposure to inhalation of airborne mites in dusty stores, warehouses, mills, etc.

Possible ætiological factors suggested by results of laboratory investigations include pulmonary helminthiasis, pulmonary spirochætosis, pulmonary filariasis, pulmonary virus infection and pulmonary acariasis.

Observations in Ceylon, initiated by the work of Carter, Wedd and D'Abrera (1944) have resulted in the isolation from the sputum of various mites in all stages of their life cycle. The mites most frequently found were species of *Tyroglyphus*, *Tarsonemus*, *Glyciphagus* and *Carpoglyphus*. Carter and D'Abrera (1946) have found a significant reduction of mites in the sputum of patients after arsenical treatment. The search for mites is a painstaking task. An equally painstaking search in controls revealed no mites in the sputum of healthy subjects, and cases of non-eosinophilic respiratory disorders (Soyso, 1949). The relatively scanty numbers of mites found in the sputum in this syndrome is comparable to the paucity of mites in cutaneous acariasis, such as scabies and acarine dermatoses, the symptoms in both instances being out of all proportion to the meagre number of mites found.

Mites have been isolated in cases of gastritis, diarrhœa, cystitis, scrotal cyst, lung abscess, cancer, etc. They have been suspected as pathogenic agents in asthma long ago, so that the recently postulated link between airborne mites and the eosinophilic respiratory syndrome is not an entirely new concept. It is, however, impossible, at this stage, to be certain that mites, even when found, are responsible either for the eosinophilia or the respiratory disturbance. But, although the syndrome continues to defy precise pathological definition, it appears to be associated with a multiple ætiology in which mites may have a possible role.

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THE HISTORY OF HUMAN CANCER

By MAURICE COPISAROW, D Sc

From the Research Laboratory, 1 Gildridge Road, Manchester, 16

SUCH compelling circumstances and instincts as want and fear exercised man's faculties and determined his actions. Medical knowledge evolved gradually as a part of corrective and, later, preventive measures to meet the hazards of man's life. Our present-day knowledge, in its ultimate analysis, may be regarded as our heritage from successive interacting cultures. The earliest medical records are found in Shen Nung's comprehensive Herbal in China,¹ the Brahmin legendary records in India² and the knowledge of Taaüt, engraved upon the columns and collected in papyri in Egypt³. These records appear to be equally remote in antiquity (*circa* B C 2500), yet each has its own distinctive features, suggesting the existence of earlier, extinct or even forgotten civilisations. The social advancement of these cultures was generally co-ordinated and disciplined by priestly castes, who, though often exploiting public ignorance, laid the foundations of medical aid and hygiene. The separation of rationalism from mysticism during ancient Greece and again in modern times ensured medical progress.

Our knowledge of the diseases of the ancients is derived from both their written records and material remains. Although no direct reference to cancer is found prior to ancient Greek and Persian writings, archæological work in Egypt and Peru (Virchow, Ruffer, Elliot Smith, Herdlicka and Moodie) reveal the existence of osteomalacia, osteoporosis and osteosarcoma among other bone deformations.

The Hebrew culture in its later arrival brought with it the mysticism of the East, the system of priestly castes and the arts and crafts of Egypt. Its medical knowledge was founded upon Egyptian, Syrian and Babylonian influences⁴ which were modified by Greek teaching and ultimately incorporated, together with beliefs and rules of social morality, into a single religious code⁵. In Hebrew writings there are many instances where the symptoms given leave no room for doubt as to the presence of malignant growth⁶. Thus (1) the case of King Jehoram, II Chronicles, xxi, 14 (Septuagint—Joram) may be identified as cancer of the rectum,⁷ (2) the affliction, referred to in Numbers xiv 37, seems to deal with cancer of the tongue. This may be compared with the case of Diocletian quoted by Cedrenus,⁸ (3) some of the Talmudic descriptions of genital diseases correspond to cancer of the uterus,⁹ and (4) the biblical description of bone diseases in Numbers, xxiv, 8, according to Rashi's commentary, provide symptoms which correspond to cancer of the bones¹⁰. Again, the biblical injunctions and regulations regarding hygiene, sex-intercourse (Leviticus, xv, 25) and circumcision are obviously designed to prevent many sex diseases, including cancer.

Prior to the time of Homer (*circa* B C 850) a mature culture had

already grown up in Greece. The Greek settlements, along the coast of Asia Minor and the neighbouring islands, with their pursuits of trade and war, brought them into contact with the Syrian, Persian, Mesopotamian and especially Egyptian cultures. However, the adverse priestly influence was less felt in Greece. Owing to the character of the people and local conditions some priests became actual protagonists of medicine, as in the case of the temple of Aesculapius at Epidaurus and that of Melampus at Argos. Greek medicine found its origin in Egyptian teachings, such as those given in the temple of Seraphis at Memphis and elsewhere. In course of time the study of medicine gradually drifted from the temples to independent philosophical schools where rhetoric, mathematics and arts were studied. These schools spread from the Ionian islands to the mainland with Athens as its centre. Here several generations of scholars laid a foundation to physiology and pathology, the practical aspect of which was approached in the light of the superficial humoral conception of that era. Thus Pythagoras (B C 580-489) who travelled extensively in Asia Minor, Phœnicia and Egypt contributed considerably with his school to physiology and hygiene. Alcmaeon of Crotona, a disciple of Pythagoras, is credited with original work in anatomy and physiology and is believed to have been the first person to dissect for the sole purpose of learning anatomy. Empedocles of Agrigentum (B C 504-443) and Democritus of Abdera (B C 494-404) contributed to physiology and anatomy. During this period Democedes of Crotona, who was taken prisoner by the Persians, acted as physician to Darius and successfully treated his wife Atossa for a tumour of the breast. Aristotle (B C 384-322) closely linked his general philosophy with the study of natural history and anatomy. His work influenced later research on physiology and pathology.

During this period cancer which was hitherto undifferentiated from benign tumours, ulcers and carbuncles, became recognised, named and studied in detail. A treatment was developed based on excision and a variety of escharotics, including arsenical ointments. A comprehensive collection of these medical studies is to be found in the *Corpus Hippocraticum* (Hippocrates of Cos, B C 460-377¹¹).

During its golden era, Greek learning followed in the wake of political and economic expansion. It penetrated into Persia, reached the gates of India and returned to Egypt changed beyond recognition. Under the Ptolomean dynasty, Alexandria, founded in B C 331 became a great cultural centre where Greek philosophy and medicine (Herophilus, Erasistratus) mingled with Hebrew theology. Great improvements were made in surgery and special attention was given to gynæcology and obstetrics. Thus, this outer perimeter of Greek culture, rather than its declining centre, became the source of inspiration. With the rise of Rome, many of the Alexandrian physicians migrated to Italy, and to such strategic towns as Pergamus, Tralles, Miletus, Smyrna and Laodicea. By B C 110 the argument between the Dogmatists and Empirics had resolved itself into a disagreement between

the supporters of the methods of induction and deduction and most men sought the middle path between them

The writings on pathology of Cornelius Celsus (B C 25-50 A D) were the most accessible during the early Roman period. Much of his description of malignant growth and its treatment can be traced to Hippocrates and his followers. He identified the gross varieties of cancer and he excised breast cancer, advising against removal of the pectoralis major¹². Archigenes of Apamea, a contemporary of Celsus, perfected the operation of amputation, carried out hysterectomies, and operated upon mammary carcinoma¹³.

Claudius Galen (131-203 A D) a native of Pergamus, Asia Minor, was educated in Alexandria, and migrated to Italy¹⁴. He was the founder of experimental physiology and pathology, and made such a presentation of the humoral doctrine that his writings dominated medical thought for more than a thousand years. According to this doctrine the body was regarded as containing four fluids—the blood from the heart, the phlegm from the head, the yellow bile from the liver and the black bile from the spleen. Any adverse mixture of these fluids resulted in disease. He considered that cancer developed from the concentration of black bile. He noticed that tumours arose in the period following suppression of the menses, and with the appearance of hæmorrhoids. These phenomena prevented the discharge of black bile, which became stagnant, resulting in cancer. Leonidas of Alexandria (180 A D) broke away from Hippocratic conservatism. He removed breast cancer extensively, cutting through healthy tissue with knife and cautery, and approached closely the modern technique of this operation.

Social and political upheavals during the succeeding centuries led to stagnation in human learning. Though familiar with the teaching of ancient Greece and Rome, the actual progress of Byzantine medicine was meagre. Its important role was in preserving knowledge and passing it on to the Arabs. Paul of Ægina (625-690) was one of the outstanding Byzantine physicians¹⁵. The exile and dispersion of Hebrew culture (Titus, Hadrian) Roman and Byzantine decadence, and a religious fervour (diverted from high ideals of morality to persecution and devastation)—all brought learning to its lowest ebb during the succeeding centuries. Intrigue and decay within the structure of the old civilisations contributed quite as much to the eclipse of knowledge (the Dark Ages) as did the incursions of Goths and Vandals across Europe and that of the Moslems from Asia through Africa into Spain.

Through the centuries—long contact of the Arabs with Jewish communities in Arabia and later with the Jewish colleges in the Persian towns of Nehardea, Sora and Pumbeditha within the Eastern Caliphate, the Arabs became familiar with metaphysics, mathematics, astronomy and medicine¹⁶. The Arabs were also influenced by Byzantine teaching through the Nestorian hospitals in Edessa (Mesopotamia)

and Djondisapour (Persia) Within a few centuries, Bagdad, Cairo, and Cordova became renowned places of Arab learning The general contribution of the Arabs to medicine consisted largely in maintaining the Greek knowledge—only in materia medica and chemistry was an advance made

Rhazes (*circa* 900 A D), a famous surgeon of that period founded his teaching on that of the Greeks He made a significant remark, "when Galen and Aristotle agree, it is obvious that their opinion is correct, but when they disagree, judgment is indeed difficult" He produced the famous work which translated into Latin under the name of *Continens* served as the standard for mediæval therapeutics¹⁷ According to Rhazes, carcinomatous growths were to be excised or completely burnt out, but if the tumour could not be completely extirpated, it was not to be incised In such cases the cautery alone was to be used Haly Abbas (*circa* 994) was a Persian physician who wrote *al-Kıtab al-Malaki* the anatomical portion of which became for over a century the teaching text in anatomy at Salerno Albucasis (eleventh century) produced the *Compendium* which included the surgery of cancer Avenzoar-ibn-Zuhr (1092-1162) a late writer of the Western Caliphate, described gastric carcinoma of the œsophagus¹⁸

Whilst Islam spread throughout the east and south, Christianity (the ethical and ethnological amalgam of Greek and Hebrew cultures), progressed in the north and west Apart from the often cruel methods of expansion, it exercised an important educational and disciplinary role upon the newly converted tribes The religious and social work was centred in the monasteries Here, as conditions became more settled, the monks extended their learning to general science and medicine In Italy and later in France, contact was made anew with ancient Greek and Roman teachings mainly through Arabic writings These experiences of the Monte Cassino monastery led to the establishment of the medical school, "Civitas Hippocratica," at Salerno about the end of the tenth century The school came under the influence of contemporary Arabic teaching, and some of the teachers such as Constantinus Africanus (eleventh century) actually received their training in Bagdad At the medical school of Bologna (*circa* 1200) an approach was made to re-establish the methods of both Erasistratus and Herophilus in the study of human anatomy by dissection

During the thirteenth and fourteenth centuries, Italian medical schools made considerable progress under Taddeo Alderotti, Mondino de Luzzi and others and they became important seats of learning for many students from outside Italy From here medical training extended to the universities of Montpellier and Paris which were influenced by Jewish physicians from the Moorish colleges of Cordova, Granada and Toledo, and by Christian physicians from Salerno¹⁹

At the end of the fifteenth century the introduction of printing exerted a great influence on the spread of learning During the Renaissance period medical sciences progressed through the teaching of

Marc Antonio Della Torre and through the dissections and drawings by Leonardo da Vinci Paré (1510-1590) gave detailed descriptions of cancer, the transition from *cancer occultus* to *cancer apertus*. His classification was still based on the ubiquitous black bile. Harvey's discovery in 1619 of the circulation of the blood, facilitated the diagnosis and treatment of cancer, but added little to the etiology of the disease. Nicholas Tulp (1593-1674) described various types of carcinoma. He regarded mammary cancer as contagious.

Andrew Vesalius (1514-1564) was one of the first to attack the theories of Galen. Francesco Peccetti²⁰ gave a detailed study of surgical methods as applied to mammary cancer. It was well known that mammary carcinoma rapidly finds its way to the axillary glands, and usually the entire breast was amputated as soon as evidence of a definite tumour presented itself. Marcus Aurelius Severinus (1580-1656) described myxosarcoma, distinguished between benign and malignant tumours of the breast and extirpated the axillary lymph nodes.

During this period Paracelsus opposed Galen's theory and claimed that cancer was caused by mineral salts in the blood. This decline of Galen's authority and the distrust of his crude theories of etiology lead to a complete demoralisation in the treatment of cancer and encouraged the abuse of arsenic and other external and internal remedies. It brought in its wake various fantastic theories and faith cures, ranging from spells to witches' brews. The basic notion seemed to be that the uglier the disease, the nastier its remedy and that the mystery of the affliction must be countered by supernatural intervention. In England anatomic teaching was not attempted until the latter part of the sixteenth century, when it was conducted by the barber-surgeons.

The development of the microscope during the seventeenth century gave a great impetus to the study of anatomy and pathology. With the discovery of the lymph-vessels (Owens 1652) came the lymph theory of the origin of cancer. It is easy to understand this belief when we take into consideration the lymphatic spread of such tumours. Helmont and others were now turning to chemical conceptions, and cancer was attributed usually to an excess of acid to be treated by alkalis.

The role of chemical and mechanical irritants in producing and aggravating neoplasms, realised from earliest times, was strengthened by Pott's observation (1775) upon the prevalence of cancer among chimney sweeps. During this period the general theory of irritability was applied to pathology (Haller, Fabre). Sauvages classified cancer among skin diseases²¹—a conception reminiscent of the earlier primitive ideas.

The construction of the achromatic microscope in Paris in 1824 opened up a new era in cancer research. In 1838 Schwann established the doctrine of cellular structure as a universal principle and discovered the nucleus and nucleolus of the cell. In spite of very careful histological studies of tumour tissues all writers were led to believe in the blastoma origin of cancer. This blastoma was assumed to develop, not from normal but from germ cells lying scattered between the tissue

elements Though burdened by this theory, the study of cancer had succeeded by 1860 in describing and classifying more accurately the main types of tumours, chiefly according to microscopic appearance ²²

Correct conceptions of histogenesis were impossible, however, until Virchow ²³ founded his cellular theory of pathology, according to which cells grew exclusively from other cells by endogenous reproduction He failed, however, to interpret correctly the formation of cancer and believed that cancer cells arose from connective tissues

Many authors attacked this theory but it was not until 1865, when Waldeyer traced the origin of cancer of stomach, liver and kidney to the epithelial cells of these organs, that the epithelial nature of carcinoma was generally accepted During this period Recklinghausen and Koster established the group of endotheliomas Recklinghausen in his work on neurofibromatosis and neural neoplasms attempted to link genetics with hereditary influences

The tendency of carcinomatous metastases to occur elsewhere and at some distance apart led to the assumption that the systemic condition which had given rise to the original cancer produced another in a new location However, it was soon observed that the metastatic foci were related to the original by virtue of lymph drainage According to Billroth —“ The carcinomatous and epithelial forms which are met with in primary carcinomata have always been found in the infection-tumours of the lymphatic glands This appears to me to speak strongly in favour of the transportation of cell-elements, for it is scarcely conceivable that fluid from a columnar epithelial cancer should be capable of causing cells of the lymphatic glands to produce columnar epithelia It is very probable that the epithelial gland-like prolongations not unfrequently grow into spaces between the bundles of connective tissue in which lymph circulates, for the tissue here offers the least resistance I cannot ignore the fact, that by our more modern methods of operating (mammary cancer) where the skin is preserved as far as possible, so as to induce the wounds to unite quickly by first intention, recurrence seems to me to take place far more rapidly ” ²⁴ Koster's observations seem to confirm that the canal-like prolongations, mentioned by Billroth, are confined to the lymphatic vessels, thus leading to the early infection of the lymphatic glands

In 1877 Cohnheim advanced the theory that tumours arose not from normal cells, but mainly from isolated embryonal cells and tissue rests This theory still holds good, but only for a few rarer tumours The last decades of the nineteenth century were thus devoted to the detailed study of the morphology of tumours and the elucidation of their histogenesis The introduction of aseptic surgery at this juncture led to the use of suppurative ligatures to remove inaccessible carcinomatous growth when the knife, cautery or corrosives were unsafe Cancer research was concerned mainly with the study of fully developed tumour tissue By the transplantation of such tissue, artificial metastases were formed and these again were studied

Thus we see that the main trend of work was directed to the pathology rather than to its surgical and therapeutical nature. Whilst the main objective in surgery was the complete removal of the growth, this was unattainable except in the case of superficial growths. Realising the essential futility of surgical therapeutics, pathologists and surgeons directed their attention to medical treatment and prophylaxis. Here again only defeat lay ahead, the more particularly since confusion between benign and malignant growths obscured any correct evaluation of the results.

The beginning of the twentieth century marks the opening of the experimental era with the systematic study of tumours throughout the animal kingdom.

Parasitic theories of malignant tumours were supported long ago by surgeons, such as Dupuytren, who believed in their infective nature. According to Borrel, a cancer cell is a symbiosis between a cell and the virus which inhabits it, and he and Fibiger (1913) and others have made many interesting suggestions as to possible methods of access of the virus to the tissues by carriers, such as nematode worms in gastrointestinal cancers, and the *acar* and *demodex folliculorum* in cancers of the skin (also in nipple and duct cancers of the breast). The fact that a long series of supposed specific bacterial infections, of fungi, yeasts and protozoal organisms have been shown not to be causal, hardly supports the infective theory of cancer. A further difficulty in accepting this theory has been the "specificity" of many tumours when inoculated experimentally, which would suggest a specific strain for each type of tumour. Less specificity, however, has been found by a number of workers on fowl tumours and fowl leukæmia, and some have suggested that one agent may produce in different animals, carcinoma, sarcoma, endothelioma, or myeloid or lymphatic leukæmia. The modern infective or virus-theory has received great support from Gye's researches, and from those of Peyton Rous and of Shope (on three experimental sarcomas, and the papilloma of "cottontail" rabbits), of McIntosh (on Rous sarcoma and tar-induced fowl tumours) and of Andrewes (on Shope fibroma and tar-stimulation, and on virus antibodies and the "latency" of virus infections). "Some who would be willing to support an infective theory for cancers of the skin, upper air-passages, gastrointestinal tract and cervix (all accessible areas and open to exogenous infection) would consider cancers of the internal organs as more likely to be due to endogenous viruses, similar in nature to enzymes or catalysts, and arising as autogenous products of some disorder of metabolism. Of interest is the theory that the cancer cell is atavistic, returning towards the primitive embryonic type of cell, with its almost indefinite growth capacity (Blair-Bell and others). There is also the theory, difficult to prove or disprove, that the cancer cell is an aberrant or anarchic type of cell, with a nuclear disease, possibly due to a gene-mutation (Lochart-Mummery)." (J Douglas Webster—*The Periodicity and cause of Cancer*, London, 1940.)

In connection with breast cancer the recent evidence as to a transmissible milk factor bridges the difference between mammalian and avian cancer and incidentally seems to undermine the whole virus theory of malignant growth. The fact that mammary excretions are brought into being and are controlled by pituitary and sex hormones, which in themselves are capable of functioning as chemical carcinogens, hardly supports a virus theory of the carcinogenic milk factor. The presence of nucleoproteins or nucleic acid in the active milk agent ²⁵ does not necessarily vindicate the virus hypothesis. It is much more in agreement with the modern assumption of associations between the chemical carcinogen and enzymic complexes in all types of malignant growth. Especially in the case of mammary tumours the virulent factor may acquire organic complexity and mobility, that is, become transmissible through the association of a chronic excess of steroid carcinogen or hormone with the embryonic cells or tissue rests. In any event, in view of recent studies of the chemistry of viruses and the function of optically active chemical complexes it would appear that the virus and chemical conceptions of cancer are not so utterly divergent from one another. They merely represent the biologist's and the chemist's points of view of one and the same set of conditions, where the simplest form of organised matter becomes synonymous with the more complex optically active chemical unit. Tumour-transmission through mammary gland excretions demonstrates the possibilities of the earlier hypotheses as regards the spread of cancer along the lymphatic canals.

In 1915 Yamagiwa, echoing the earlier observations of Pott, demonstrated the cancer-causing properties of coal tar. Later work on the action of wood tar, barley bristle and other irritants on rats, revived the old irritation theory of tumours. The mechanical aspect of this problem was, however, soon overshadowed by the isolation of specific chemical carcinogens from various tarry pyrolytic products and later, by the synthesis of an ever-increasing number of carcinogenic unsaturated hydrocarbons (Butenandt, Kennaway, Dodds, Cooke, Fieser *et al*).

The close constitutional link between the synthetic carcinogens and many steroid metabolites, capable in themselves of causing malignant growth, provides a common metabolic ground for synthetic and spontaneous cancer. The further extension of synthetic carcinogens to mustard oils and certain azo-dyes seems to link these substances with the steroid forms as possessing in common a reactive point K, a region of high electron density, at which the association with enzymic complexes takes place ²⁶. The fact that such inductive agents as radium emanations, X-rays and other radiations may induce metabolic distortions characterising cancer, widens still further the range of carcinogenic influences.

The work of Warburg, Hopkins and others on suppressed enzymic activity in relation to malignant growth, especially glycolysis and the equilibrium of SH-SH-SS, constitutes an important contribution to the etiology of cancer. Again, the transition of steroid hormones into

the essential cell constituent—cholesterol, as well as chromosomal changes and gene mutation induced by various carcinogens, connects the resulting functional and structural changes and throws much light upon the genetic aspect of carcinogenic action as related to the somatic cell

The present trend in research seems to converge on the etiology of cancer and the elaboration of corrective, and, better still, preventive measures ²⁷

In summing up, we find that in medicine as in other spheres of human activity there is a certain continuity or gradual development. Thus, modern osteology may be traced back to the symbolic bones of the Hindus, the Talmudic "Luz"—the magic bone of resurrection—and beyond that the miraculous scapula of the Far East. In the case of cancer, the modern aseptic surgery and the radium and X-ray treatment of tumours must be viewed as direct descendants of the antique cautery, the knife and the escharotics. The present contact and inductive carcinogens and the virus theory find their inception in the earlier assumptions on cancer-causing irritants and parasites. The modern transmissible milk factor of breast cancer is not too remote from Tulp's conception of mammary cancer as being contagious (seventeenth century)

The mediæval stress upon mineral salts or acidity as a significant factor in the etiology of cancer is not strange to the modern investigator who seeks to establish the relationship of the geographical distribution of human cancer to the type of soil, the mineral components of cancerous to those of normal tissue, and ratio of K—Na to Ca, K to Na and those of K isotopes

Again, Hippocrates and Galen's humoral black bile theory is not utterly absurd to one who regards the protracted distortion of steroid hormonal equilibria as an important carcinogenic condition

REFERENCES AND NOTES

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- ² About 500 B C the newly evolved contributions of Greek thought began to filter eastwards. Not only Persia but India and even China were influenced by this diffusion which followed the slow-moving, transcontinental, commercial routes of the ancient world. While it is possible to discover traces of primitive medicine in Hindu literature, prior to the First Christian Century, the first evidence of what might be termed a system of medicine is traceable to a later date (Charaka second century A D, Susruta between sixth century B C, and fifth century A D, Vagbhata circa A D 625)
- ³ The knowledge of Taaut, engraved upon the columns and collected in papyrus entitled *Embre* or *Scientia Causalitalis* which served as a medical code for the Egyptians, according to Diodorus. Edwin Smith Papyrus written seventeenth century B C as a copy of an earlier work composed circa 2500 B C available in a modern reprint and English translation by J H Breasted—*The Edwin Smith Surgical Papyrus* (1930), Chicago *Papyrus Ebers* (circa 1550 B C) on Pharmacology, C P Bryan (1930), London

- ⁴ The earlier medical records are found in the Pentateuch, the first four books of which are considered synchronous with the *Iliad*—850 B C ending about 150 B C
- ⁵ The Talmud (specifically the Mishnah plus Gemarah) a work occurring in two issues—*The Jerusalem Talmud* (fourth century A D) and the *Babylonian Talmud* (fifth century A D)
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- ¹⁶ The Arab tolerance towards Jews and the encouragement given to their scholarship and crafts made the Jewish contribution an integral part of Arab culture, and Judeo-Arabic would be a more accurate assessment of that culture Apart from the great theological scholars, the *Gaonim* of Babylonia, the culture of the dispersed Jews of that period, is represented by Philo, the philosopher of Alexandria 40 B C, Samuel, the astronomer of Nehardea circa third century A D, Zedekiah, physician ninth century, Solomon ibn Gabirol, poet and philosopher eleventh century, Rashi, theologian eleventh century, Jehudah Halevi, physician and poet eleventh to twelfth centuries, Abraham ibn Ezra, theologian eleventh to twelfth centuries, Rabbi Benjamin of Tudela, traveller and geographer twelfth century, and Moses ben Maimon (Maimonides) physician and philosopher twelfth century
- ¹⁷ RHazes (1510), *Ad Almansorem libri decem* Venice
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- ¹⁹ Henri de Mondeville (circa 1260-1320), professor of anatomy, surgery and medicine at Montpellier Guy de Chauliac—followed his predecessor Mondeville in regarding anatomy as the proper foundation for surgery *Chirurgiae tractatus septem cum antidotario* (written 1363, published in Venice 1470)
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NEW BOOKS

Modern Trends in Neurology Edited by ANTONY FEILING, B A , M D , F R C P
Pp lx+717, with 202 illustrations London Butterworth 1951 Price 63s

Contributions from more than 20 authorities in this country and the United States have been brought together in this book to form an up-to date account of some of the subjects in neurology in which valuable advances have been made in recent years

The editor stresses the point that his selection of material has been based on the progress which has been made in the different aspects of neurology, and though such selection has necessarily been a limiting factor to the completeness of the work, the scope of the book as it appears is immense

All the contributors are of a very high standard, but Denny Brown's chapter on the Frontal Lobes and their functions is quite outstanding It is the longest chapter in the book and gives a very complete account of present-day work, together with all the ideas and experiments which have gone before The chapter on Intracranial Tumours by Northfield and Russell and Intracranial Aneurysms by Meadows likewise deserve special mention for their interest and detail

Bull's chapter on Diagnostic Neuro-radiology is a very welcome inclusion with its fine illustrations

These, with all the other excellent sections in the book, packed with valuable information, make it an essential part of the equipment of every neurologist

Primary Carcinoma of the Liver By CHARLES BERMAN, M D , B CH Pp xvi+ 164,
with 83 illustrations London H K Lewis 1951 Price 35s net

This is an interesting monograph on what might be called geographical pathology, as it is primarily a study of malignant disease of the liver as it occurs in the Bantu race of Africa The author shows how this disease is the most common form of malignancy amongst this people, and discusses the question of genetic as against environmental causes He finds that cirrhosis of the liver is also a common feature amongst this race, and that is related to food conditions which in many cases are highly defective Hæmatochromatosis also seems to be frequent in South Africa He also draws attention to a similar frequency of this disease amongst races in the Indo China region With regard to the disease itself he recognises certain groups mainly on their clinical features

The book is well illustrated and furnished with an extensive bibliography As Sir Ernest Kennaway mentions in his Foreword, a work of this nature should stimulate similar observations amongst other races We might in that way get useful information as to environmental factors in the cause of cancer

The Rational Treatment of Catarrh By W ANNANDALE TROUP, M C , M D , CH B
Pp 85, with 8 illustrations London Chatterson Ltd 1951 10s 6d

This book deals with the treatment of nasal catarrh and sinusitis with infra-red and the intranasal application of ultra-violet light by a Kromayer Mercury Vapour Lamp Special applicators are shown for both nasal cavities and nasopharynx

The physiological effect of this treatment is indicated, but it is based upon theoretical rather than clinical experience

This form of therapy is associated more with tubercular infection of the nose than suppurative sinusitis—in the latter condition favourable results have rarely been obtained

Heart Disease Its Diagnosis and Treatment By EMMANUEL GOLDBERGER
Pp 651, with 90 illustrations London Henry Kimpton 1951 Price 70s

The publication of a textbook on Heart Disease by an eminent cardiologist is almost a quarterly event. The most recent addition by an author who is better known on this side of the Atlantic for his pioneer work on unipolar lead electrocardiography, follows the accepted pattern for such books.

The preface consists mainly of an apologetic admission that most cases of cardiovascular disease can still be diagnosed by the clinician without any of the modern ancillary tests such an admission thereby justifies the material to follow, although mechanical tests are in no way neglected. An orderly succinct somewhat dogmatic presentation of all aspects of cardiology follows, the whole of which is very readable.

Criticism might be expressed that only five pages are devoted to functional disorders of the heart. The treatment of this latter condition by the Freudian concept of "transference" is not acceptable to most physicians, also, is pregnancy to be discouraged "if mitral stenosis is present?"

Graduates seeking guidance on cardiac disorders common or rare, will find this book of value.

Growth and Development of Children By E. H. WATSON, M.D., and G. H. LOWREY, M.D. Pp 260, with 54 illustrations Chicago Year Book Publishers 1951 Price \$5 75

The welcome emphasis now being placed on the study and promotion of optimal health in childhood is being reflected by the publication of an increasing number of books on various aspects of growth and development. This book is a product of the Pædiatric Department of Ann Arbor. It is a general survey of growth and development from conception to maturity and is intended for students, post-graduates and practitioners, rather than research workers. Emanating from a leading pædiatric centre, under the ægis of Professor James L. Wilson, it can be strongly recommended as a simple, practical portrayal of the subject, and it contains an extensive bibliography for those who wish more detailed information.

The Medical Annual 1951 Edited by Sir HENRY TIDY and A. RENDLE SHORT
Bristol John Wright 1951 Price 27s 6d

The 69th edition of the *Medical Annual* follows the usual lines. Articles of importance in every field of medicine are abstracted, but special attention is given to those of outstanding importance such as the chronic rheumatic disorders, anti-coagulants and chest surgery. The section of Legal Decisions is of special interest. One curious finding that is fully discussed is that the change of control of hospitals does not constitute legal "nationalisation."

The book is very fully illustrated by plates, many of which are in colour. The present edition of the *Medical Annual* amply fulfils the purpose for which it is intended.

Between Life and Death By HARLEY WILLIAMS, M.D., D.P.H. Pp 288 London Jonathan Cape 1951 Price 15s net

This is a third series of biographies by an author who has already made a name for himself in *Doctors Differ* and *The Healing Touch*. The biographies are mostly medical but include one or two whose contact with medicine is indirect. The series of portraits include John Hunter, J. Y. Simpson, Pasteur, Lister, Freud, Barnardo, Truby King and Banting, also the originators of ether anaesthesia, Mrs Eddy, Margaret McMillan and Ehrlich. These pictures are sympathetically drawn and beautifully written. Dr Harley Williams has proved himself a master of this type of record, and this new series will be welcomed by the medical profession.

The Treatment of Varicose Veins By S M RIVLIN Pp viii+56, with 5 plates and 25 figs London William Heinemann 1951 Price 10s 6d net

This is a concise monograph with an essentially practical outlook. A useful classification is illustrated in Figs 1-10. Well-established lines of treatment are described. Ligation is advocated in all cases where there is a retrograde flow of blood within the vein, and the elastoplast bandage is recommended for varicose ulcer.

Alice and the Stork By EGBERT MORLAND Pp 87, illustrated London Hodder & Stoughton 1951 Price 7s 6d net

This is the life story of Alice Gregory who was one of the creators of the training school for midwives at Woolwich. It is compiled from the data of Miss Maud Cashmore who was another of the pioneers. The story also includes the struggle to raise the status of the midwife—an interesting tale.

The Isocortex of Man By P BAILEY and G VON BONIN Pp xi+301, fully illustrated Urbana Univ of Illinois Press 1951 Price \$5 paper, \$6 cloth

This is an important study of the human brain. The authors have summarised the history of the subject and have a wide experience of the brains of the primates. They describe the superficial sutures of the brain and the details of serial sections of different parts. Considerable attention is given to the various cortical areas, intercortical connections, afferent and efferent connections and to the functional significance of various parts. The last chapter is devoted to the functional significance of the anatomic and histological findings. A large bibliography is included.

This authoritative work is likely to become a classic.

The Story of St Luke's Hospital—1750-1948 by C N FRENCH, C M G, C B E Pp 212 London Heinemann 1951 Price 8s 6d net

In 1950 six gentlemen of the City of London met to discuss a project for establishing a hospital for the care of poor lunatics. The result was the founding of one of the earliest of the voluntary hospitals. The book goes on to describe the progress of the hospital and the improvement in the lot of the insane. It is full of detail and accounts of the state of affairs at various stages. The old hospital closed in 1916 and some years later the management undertook to provide for functional and organic nervous disorders at Woodside. Well written and interesting, this is a record of medical progress.

Wonderfully Made By A RENDLE SHORT, M D, F R C S Pp 159, illustrated London Paternoster Press 1951 Price 6s net

Professor Rendle Short has written a short book for the layman on the human body and some modern discoveries about its structure and functions. He touches on several systems of the body, gives an account of vision and hearing, and the development of the embryo, and there is a long chapter on the problem of Man's origin. The book is one which should appeal to the intelligent layman.

The Essentials of Modern Surgery Fourth Edition, edited by R M HANDFIELD-JONES, M C, M S, F R C S, and Sir ARTHUR E PORRITT, K C M G, C B E, M A, M CH, F R C S Pp xv+1263, with 641 illustrations Edinburgh E & S Livingstone 1951 Price 55s net

The fourth edition of this well known textbook has been revised and brought up to date after an interval of twelve years, and although new chapters have been added, particularly on antibiotics, the book has not increased in size. Random sampling indicates that the volume has retained its reliability as a source of information to students, to whom it may be confidently recommended. Perhaps in the next edition further improvement in the illustrations will be possible, particularly in some of the photographs.

Surgery of the Stomach and Duodenum By CLAUDE E WELCH Pp 349, with 79 illustrations Chicago The Year Book Publishers 1951 Price 65s net

This is the first of a series of "Handbooks of Operative Surgery" the professed object of which is "to present simply but vividly the step by step technic of the more common surgical operations" This volume is a successful and promising start

The author is a surgeon in the Massachusetts General Hospital and his preferences reflect the practice in that hospital, but there is no undue emphasis on personal opinions and the important alternative techniques are well described Sections on pre- and post-operative care are included, and the whole is well balanced The text is concise and practical but fundamental principles are never forgotten or obscured by the detail The 79 full-page plates represent more than 450 excellent line drawings, each illustrating a stage of the technique described on the opposite page

This book will be welcomed by surgeons in training, but it is by no means elementary and can be warmly recommended to more experienced surgeons

The Postnatal Development of the Human Cerebral Cortex Vol IV The Cortex of the Six-Month Infant By J LEROY CONEL Pp viii+191, with 7 tables and 108 full plates Harvard University Press (London Geoffrey Cumberlege) 1951 Price 82s 6d net

The fourth volume of this important work is concerned with the cerebral cortex of the six-month-old child as demonstrated by cresyl violet, Cajal, Cox-Golgi and Weigert methods of staining The format is the same as in the three previous volumes, which described the brains of newborn, one-month and three-month-old children

An effort is made to reduce the main features of each cortical region to mathematical terms by measurement of laminar thickness together with enumeration and calibration of the cells and fibres in every layer It is doubtful whether measurements to the third decimal place in millimetres have any significance for such indefinite structures as the cortical laminæ, and unfortunate that many of the photomicrographs fail to demonstrate the features for which they are intended

The use of multiple staining methods in the study of the cerebral cortex is to be welcomed, though the evaluation of the results must depend on the degree of variation found in brains of the same age, a feature which receives scant attention

This volume is produced in excellent style and as an integral part of a larger series it has a special importance

Surgical Forum—American College of Surgeons Pp 665 London W B Saunders 1951 Price 50s net

This volume represents the papers presented at the Surgical Forum of the Clinical Congress of the American College of Surgeons, 1950 The forum provides an opportunity for young research workers to bring their experiments before the notice of those attending the meetings of the College, and the reviewer can testify to the outstanding success of the arrangement It is natural that the papers, which cover the whole field of surgery, are not all of a high standard, but it is important that the young workers be given an opportunity of communicating their views, and now the American College of Surgeons has published the short papers and abstracts of the longer ones Naturally such an accumulation of information on many different subjects does not lend itself to review, but the American College is to be congratulated first on the introduction of the surgical forum and secondly on making it readily available in this form to surgeons throughout the world

The Nature of Disease Institute By G E R McDONAGH, F R C S Pp lvi+457 London Heinemann 1951 Price 21s net

The author remarks that he is compelled to publish in this form because the weekly journals are closed to him The material is thoroughly unorthodox

NEW EDITIONS

Surgical Nursing and After-Treatment By M C RUTHERFORD DARLING, M D, M S, F R C S, and T E WILSON, M D, M S, M S C, F R C S, F R C S E Tenth Edition Pp ix+630, illustrated with 188 figures London J & A Churchill 1951 Price 6s

This popular and successful textbook which has held the field for over thirty years has been brought thoroughly up to date It contains a great deal of useful information in an attractive form, everything in fact which the surgical nurse requires to know The present edition maintains the standard of its predecessors and can be strongly recommended

The Pharmacology and Therapeutics of the Materia Medica By WALTER J DILLING, M B, CH B, M P S Nineteenth Edition Pp xxxii+598 London Cassell & Company 1951 Price 21s net

This volume, like its predecessor, provides both students and practitioners with the recent views on the pharmacological actions, modes of administration and relative therapeutic merits of modern drugs This nineteenth edition has been thoroughly revised to conform with the official preparations of the *British Pharmacopæia of 1948* It can be well recommended

Black's Medical Dictionary By J D COMRIE and W A R THOMSON Twentieth Edition Pp x+1013, with 417 figures and 16 plates London A & C Black 1951 Price 30s net

The first edition of this popular book appeared in 1906 under the editorship of the late Dr J D Comrie, and since then over 150,000 copies have been issued The present edition has been very extensively re-written and reset and many of the illustrations have been changed The general arrangement and plan of the work remains the same As a reference book it aims to occupy a position between a technical dictionary and a guide to the lay treatment of the commoner ailments This useful work seems likely to continue its well deserved popularity

The Early Diagnosis of the Acute Abdomen By ZACHARY COPE, B A, M D, M S, F R C S Tenth Edition Pp xv+270, with 39 illustrations London Oxford University Press 1951 Price 15s net

There is no essential change in the latest edition of this now famous little book apart from slight alterations in the text and the addition of one new radiograph As before, this book endeavours to help in the diagnosis of one of the most difficult and sinister conditions in medicine—the acute abdomen

A Pathology of the Eye By EUGENE WOLFF Third Edition, edited by EUGENE WOLFF Pp 364, with 318 illustrations London H K Lewis Ltd 1951 Price 55s net

Eugene Wolff's *A Pathology of the Eye* has for long been the foremost English work on general ocular disease The third edition maintains the standard of its predecessors The excellent illustrations have always been a prominent feature and these have been increased to the extent of one hundred The subject-matter has been brought up to date and questions of recent interest discussed with the author's customary conciseness His opinions, as on Retro lent al Fibroplasia, are dogmatic, but this is a virtue in a book which "is intended as an introduction to a subject whose essentials most Students and Ophthalmic Surgeons find it difficult to come by"

Medical Disorders of the Locomotor System By E FLETCHER Second Edition
Pp xii+884, with 337 illustrations Edinburgh E & S Livingstone 1951
Price 60s net

Interest in the rheumatoid diseases has been stimulated by the discovery of the action of cortisone and A C T H and the recent advances in our knowledge arising from this discovery have been incorporated in the new edition of this book. In addition to a chapter on Cortisone and A C T H new sections have been added on pain, physiology and pathology of bone, synovial fluid, synovial mucin, psychiatric aspects of locomotor disorders and hydrotherapy. The second edition maintains the high standard set in the first edition published in 1947.

BOOKS RECEIVED

- BOWLEY, AGATHA H, PH D Child Care
(*E & S Livingstone Ltd, Edinburgh*) 10s 6d net.
- BRAASCH, WILLIAM F, M D, and EMMETT, JOHN L, M D Clinical
Urography An Atlas and Textbook of Roentgenologic Diagnosis
(*W B Saunders Company, London*) £6, 5s
- BULL, H CECIL H, M A, M B, M R C P X-ray Interpretation Second
Edition (*Oxford University Press, London*) 25s net
- BURROWS, H JACKSON, M D, F R C S, F R A C S Treatment by Manipulation
Second Edition, Fully Revised (*Eyre & Spottiswoode, London*) 12s 6d net
- Central Council for the Care of Cripples Summary of Legislation and
Directory of Organisations for the Care of the Physically Handicapped
(*William Heinemann (Medical Books) Ltd, London*) 5s 6d net
- Fellowship Examination Papers for the Diplomas of the Royal College of
Surgeons, Edinburgh 1947-51 (*E & S Livingstone Ltd, Edinburgh*) 5s 6d net
- FULTON, JOHN F, M D Decompression Sickness
(*W B Saunders Company, London*) 42s 6d
- HUBBARD, L RON Dianetics The Modern Science of Mental Health
(*Derricke Ridgway, London*) 30s net
- KROGER, WILLIAM S, M D, and FREED, S CHARLES, M D Psychosomatic
Gynecology (*W B Saunders Company, London*) 40s
- MARTIN DOYLE, J L C, M R C S (ENG), F R C P (LON), D O (OXON) A
Synopsis of Ophthalmology (*John Wright & Sons Ltd, Bristol*) 20s
- MOLOY, HOWARD C, M D, M S C Evaluation of the Pelvis in Obstetrics
(*W B Saunders Company, London*) 12s 6d
- MONRO, THOMAS KIRKPATRICK, M A, M D, LL D The Physician As Man
of Letters, Science and Action Second Edition
(*E & S Livingstone Ltd, Edinburgh*) 21s net
- MOORE, ROBERT ALLAN A Textbook of Pathology Second Edition
(*W B Saunders Company, London*) 63s
- MURRAY, J BARRIE, M A, M D (CANTAB), M R C P Some Common Psycho
somatic Manifestations Second Edition
(*Oxford University Press, London*) 17s 6d net
- OGILVIE, ROBERTSON F, M D, D S C, F R C P E D, F R S E Pathological
Histology Fourth Edition (*E & S Livingstone Ltd, Edinburgh*) 40s net
- Edited by SANDWEISS, DAVID J, M D, F A C P Peptic Ulcer
(*W B Saunders Company, London*) 75s
- THOMSON, A P, M C, M D, CH B (BIRM), F R C S (LON), LOWE, C R, M D,
CH B (BIRM), M R C S (ENG), L R C P (LON), D P H, and MCKEOWN,
THOMAS, B A (B C), PH D (MCGILL), D PHIL (OXON), M D (BIRM), M B,
B S (LON) The Care of the Ageing and Chronic Sick
(*E & S Livingstone Ltd, Edinburgh*) 7s 6d net
- TOWN, ARNO E, M D Ophthalmology (*Henry Kimpton, London*) 70s net
- WHITING, MAURICE H, O B E, M A, M B, B CH (CANTAB), F R C S
Ophthalmic Nursing Sixth Edition (*J & A Churchill Ltd, London*) 8s 6d net

Edinburgh Medical Journal

February 1952

ON OCCLUSION OF THE ABDOMINAL AORTA

By CATHERINE C BURT, B Sc, M B, Ch B, Sir JAMES LEARMONTH, K C V O, C B E, Ch M, F R C S E, and R L RICHARDS, M D, M R C P E

(From the Department of Surgery, University of Edinburgh)

PART I—INTRODUCTION

Historical Aspects—In 1814 Robert Graham of Glasgow reported a "case of obstructed aorta" The case which he described was undoubtedly one of coarctation, but in the discussion he mentioned a museum specimen which belonged to Mr Allan Burns in which "the aorta is plugged up by a laminated coagulum, just above the bifurcation of the iliacs, into both of which this substance extends" This has been accepted by most authorities as the first mention of occlusion of the aortic bifurcation, but the condition was certainly recognised at an earlier date and had been described by, among others, Severinus (1632) and Fantonus (1679) In 1818, at a meeting of the Faculty of Medicine in Paris, Goodisson of Dublin reported a case of obliteration of the lower part of the aorta associated with calcification Details of the case are not given, but it is presumably that which he described in the Dublin Hospital Reports of the same year His observations were made on a female anatomical subject, the clinical history was not available The aorta was found to be obstructed from the origin of the inferior mesenteric artery to the bifurcation, the occluding mass extended into the iliac arteries, on the left as far as the bifurcation of the common iliac and on the right for half the length of the common iliac The wall of the occluded portion of the aorta is described as "like a sheath of bone" The obstruction was of long standing, and the mammary, lower intercostal, ovarian, lumbar and circumflex iliac arteries were enlarged and tortuous The intestines and abdominal viscera were healthy and the lower limbs were described as normal (Goodisson, 1818a and b) According to Hesse (1921), Allibert (1828) described aortic embolism in 2 children aged 3 and 3½ years respectively the first well-documented case of occlusion of the aortic bifurcation, however, is that reported by Barth (1835) The patient was a woman of 51 with an enlarged heart and an irregular pulse, who had had repeated attacks of hæmoptysis Swelling appeared and pain was felt first in the right lower limb and some months later in the left At

autopsy mitral stenosis was found, below the origins of the renal arteries the aorta was obstructed by a clot which extended into both iliac arteries and into their branches. Barth's paper contained a detailed consideration of the pathological nature of the occlusion and of the anatomy of the collateral circulation to the lower limbs.

During the latter half of the nineteenth century a number of further cases were reported, and in 1898 Welch was able to find 59 cases of occlusion of the abdominal aorta by embolism or thrombosis. By 1921 Hesse could collect 72 cases. Since then the number of published cases has increased greatly and no useful purpose would be served by an attempt to review them.

In the majority of the reports up to and including that of Hesse, cases of embolism and thrombosis were considered together because in many cases it was difficult to decide which of these two processes was primarily responsible for the occlusion. In 1911 Labey performed the first successful embolectomy, and two years later Bauer (1913) removed an embolus from the aortic bifurcation and thereby restored the circulation to the lower limbs. It then became important to distinguish between embolism and thrombosis, and this is reflected in the papers which have been published since that time, most deal with either embolism or thrombosis.

Albright and Leonard (1950) have recently reviewed the literature on embolism of the abdominal aorta. Their material consists of 193 reported cases of which 26 were successfully treated by embolectomy, but their list of cases certainly does not include all the published cases of embolism and probably includes some cases of thrombosis. The number of published cases of thrombosis of the abdominal aorta does not give a true indication of its incidence. Until Leriche (1940, 1946) drew attention to the fact that thrombosis of the aortic bifurcation can occur insidiously and may produce only mild symptoms referable to the lower limbs and to sexual function in the male, it had always been assumed that the condition was associated with a dramatic onset similar to that observed in cases of embolism, and that it was almost invariably fatal. Within recent years improved surgical technique and the availability of potent anticoagulant drugs have tended to focus attention upon the treatment of cases of embolism and thrombosis, and the events which follow the lodgement of an embolus or the development of an intra-arterial thrombus have been somewhat neglected. There may be some justification for this attitude for it is difficult to add anything to the description given by Welch (1910) in his masterly article. Nevertheless our knowledge of vascular physiology is considerably greater than it was forty years ago, and we believe that the time is opportune for a reconsideration of the clinical features which follow occlusion of the abdominal aorta. As an introduction to our clinical observations we shall consider certain anatomical, physiological and pathological aspects of the problem.

Anatomical Aspects—Normally the abdominal aorta extends

from the aortic opening in the diaphragm opposite the twelfth thoracic vertebra, to the fourth lumbar vertebra. It is formed by fusion of the two primitive dorsal aortæ, its length in any particular subject depending upon the extent to which fusion of these two primitive arteries has taken

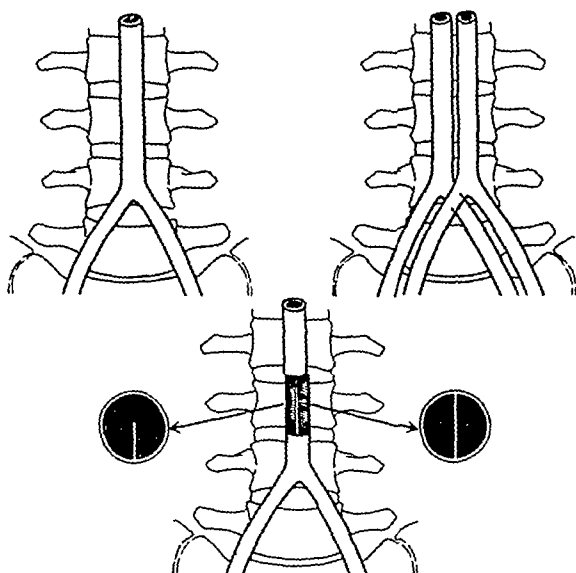


FIG 1—Upper left normal anatomy of abdominal aorta. Upper right reduplication of abdominal aorta and its bifurcation. Below possible sub divisions of single abdominal aorta.

place. Thus its division into the two common iliac arteries may be delayed to the level of the fifth lumbar vertebra, or may occur as high as the second lumbar vertebra. Sometimes the primitive dorsal aortæ fail to fuse, and "double aorta" is present, sometimes the adjacent walls of the primitive dorsal aortæ are not absorbed, and a more or less complete septum persists throughout the length of the vessel (Fig 1). It is odd that neither of these rare anomalies leading to narrowing has been recorded in association with pathological blocking. Normally also the aorta narrows rather suddenly after it has discharged its important abdominal duty of giving off the celiac and superior mesenteric arteries, but that is a level where the rapid arterial blood flow tends to prevent the lodgement of an embolus or the growth of a thrombus. Rarely a congenital narrowing of the abdominal aorta is present (Maycock, 1937). One other developmental anomaly is of clinical importance. Sometimes the bifurcation of the abdominal aorta consists of one common iliac artery and one internal iliac artery, the

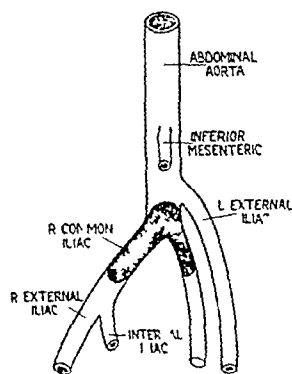


FIG 2—Abnormal aortic bifurcation into common and internal iliac arteries.

external iliac artery on the abnormal side arising from the aorta at a higher level. When such a bifurcation is obstructed, it is possible for the circulation of one lower limb to be preserved (Fig. 2)

Physiological Aspects—The function of the abdominal aorta is to nourish the viscera and the lower limbs. It is said that the abdominal aorta—or at least its lowest segment—may rapidly diminish in calibre as a result of arterial spasm. We have never seen the aorta of an adult react to handling or to incision in this way, and we doubt if its wall contains a sufficient proportion of muscle fibres to make it possible. The clinical evidence for aortic spasm is the occasional occurrence of transient complete paralysis of both legs in patients suffering from thrombo-angitis obliterans and in certain cases of pseudo-embolism to which we shall refer, but this is probably due to spasm of the common, external and internal iliac arteries which have more muscular walls.

Pathological Aspects—For practical purposes occlusion of the aortic bifurcation may be due to thrombosis, to embolism or to a combination of these two processes. Thrombosis occurs secondary to disease of the vessel wall, like any other artery the aorta may be the site of atheroma. That thrombosis does not occur more frequently on an atheromatous aortic ulcer is due to the rapid rush of blood over it, and it is understandable that blocking of the aorta by thrombus as a rule begins in the common iliac arteries, the calibre of which is smaller than that of the aorta, and extends proximally up to and even higher than the bifurcation. Less commonly, occlusion of the abdominal aorta may be due to thrombosis occurring in the sac of an aneurysm of either the dissecting or saccular type. Thrombosis of the abdominal aorta associated with syphilitic aortitis has been reported by Ronald and Leslie (1940) and by Greenfield (1943). Rarely thrombosis may follow pressure upon the aorta from without, Hesse (1921) reviewed 3 cases in which thrombosis was due to pressure by tumours, and Pinkerton (1948) described a case in which a thrombus formed in the aorta where it was compressed by a large osteophyte from the lumbar vertebræ. A large embolus may lodge in the aorta and occlude the bifurcation by being compressed into the much narrower common iliac arteries. Consecutive thrombosis proximal and distal to the clot completes the block and, much more importantly, makes it irreversible. Such emboli originate most often in the heart, either from a thrombus in a fibrillating left auricle or from a mural thrombus formed on the endocardial surface of a myocardial infarct. Paradoxical emboli have their origin in the systemic veins and reach the arterial circulation through a defect in either the interventricular or the interatrial septum. Thrombi which form in the pulmonary veins may become detached and may be swept into the left side of the heart and thence into the aorta. A partly thrombosed aneurysm or a thrombus formed on an atheromatous or syphilitic plaque in a more proximal segment of the aorta is another possible source of an embolus at the bifurcation. Among rare types of emboli which have been recorded at the aortic bifurcation

are vegetations from an anomalous aortic valve, a clot from a partly thrombosed ductus arteriosus, a portion of a myxomatous tumour of the heart and a 0.45 in calibre bullet

Both sudden and gradual types of occlusion can be recognised. Sudden occlusions are usually due to embolism and are associated with an abrupt onset of symptoms indicating acute and severe ischæmia of the lower limbs. Gradual occlusions are usually thrombotic in nature and the time at which the obstruction becomes complete is often difficult to determine. A patient with this latter type of lesion presents symptoms which, at first, may not even suggest the possibility of a vascular disturbance, only on clinical examination is it discovered that there is occlusion of the abdominal aorta. Occasionally it is possible to recognise a third group which may be described as "acute on chronic". Patients in this group are either known to have suffered from occlusive vascular disease of the lower limbs for some years, or give a history which indicates that this has been so, subsequently a sudden incident occurs in which a major proximal vessel, often the aortic bifurcation, is occluded.

Collateral Circulation—All the pathological processes we have mentioned reduce the amount of blood passing through the aorta, and we must enquire if there are alternative routes by which blood may reach the viscera and the lower limbs. In favourable circumstances, and the favour is time, both the viscera and the limbs can be adequately nourished when the aorta itself and the origins of its visceral branches are occluded.

Visceral Collaterals—In 1863 the existence of a subperitoneal arterial plexus was described in detail by the great Edinburgh anatomist, Sir William Turner, when he was Dr Turner and a demonstrator in the Department of Anatomy. His summary was as follows—

(1) That in the subperitoneal fat and areolar tissue a system of anastomosing arteries exists of greater extent and importance than has been hitherto generally recognised.

(2) That there is a much greater amount of communication between the different branches of the abdominal aorta than is commonly supposed.

(3) That not only is it possible to inject the arteries of the abdominal wall from those of the viscera, but that to some extent the blood vessels of one viscus may be injected from those of another, and this not through the main trunk from which they both proceed, but through their mutual communications with an intermediate set of anastomosing arteries.

A case showing the functional capacity of these communications between somatic and visceral vessels was published in 1869 by John Chiene, later Professor of Surgery in the University of Edinburgh, when he too was a demonstrator in the Department of Anatomy.

There was complete obliteration at their origins of the cœliac, superior mesenteric and inferior mesenteric arteries, and the viscera were supplied thus stomach, liver, spleen, pancreas and duodenum from left intercostals, left renal and suprarenal arteries and left lumbar arteries, cæcum and ascending colon, from right subcostal artery, remainder of intestines, from internal iliac arteries, through a large plexus surrounding the rectum, principally from a branch of the right internal pudendal which joined directly with the right branch of the superior rectal artery (Fig 3) The efficacy of the third of these anastomotic systems depends on the existence of an anastomosis between the

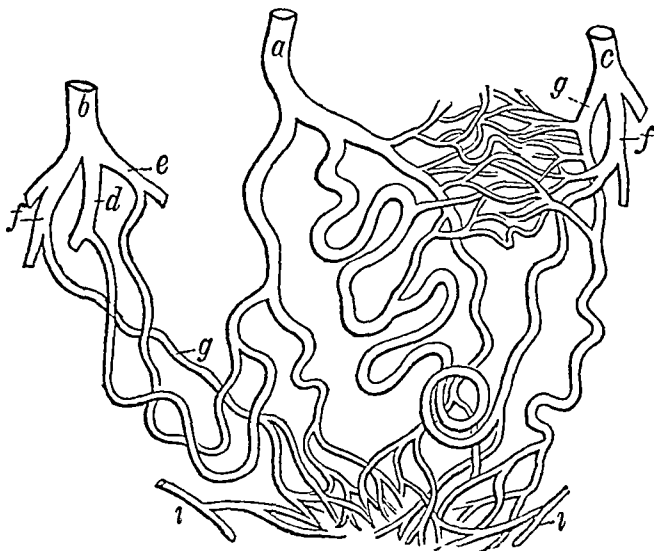


FIG 3—Diagram of pelvic plexus, seen from behind, the sacrum having been removed (a) Superior rectal (b) Left internal iliac (c) Right internal iliac (d) Sciatic (e) Gluteal (f) Internal pudendal (g) Middle rectal (z) Internal pudendal in perineum, giving off inferior rectal (After Chiene, 1869)

left colic branch of the inferior mesenteric artery, and the left branch of the middle colic derived from the superior mesenteric artery Sometimes this anastomosis is absent in man, and it is normal for it to be absent in ruminant animals

Somatic Collaterals—When the aorta is blocked at its bifurcation, blood reaches the lower extremities in two ways (1) through the communications between the terminal branches of the inferior mesenteric artery and the branches of the internal pudendal, superior and inferior gluteals, obturator and circumflex arteries (Fig 4) Recently Lindstrom (1950) demonstrated the circulation through these collaterals in the living subject In 2 cases in which the aorta was occluded by a thrombus which did not extend as high as the origin of the inferior mesenteric artery, he showed by aortography that blood was passing to the lower limbs by way of the inferior mesenteric artery and the anastomosis between the superior rectal artery and the middle rectal branch of the internal iliac, the femoral artery was refilled through the anastomoses between the obturator and internal pudendal arteries and

the medial femoral circumflex arteries (2) By purely somatic channels which include an *anterior* route, by which the superior epigastric artery communicates with the inferior epigastric, and a *posterior* route, by which the lowest intercostal and the lumbar arteries arising above the block link up with the ilio-lumbar, deep circumflex iliac, and superior gluteal arteries distal to it (Fig 4) In the female, the ovarian artery also contributes to this anastomosis These vessels may seem to

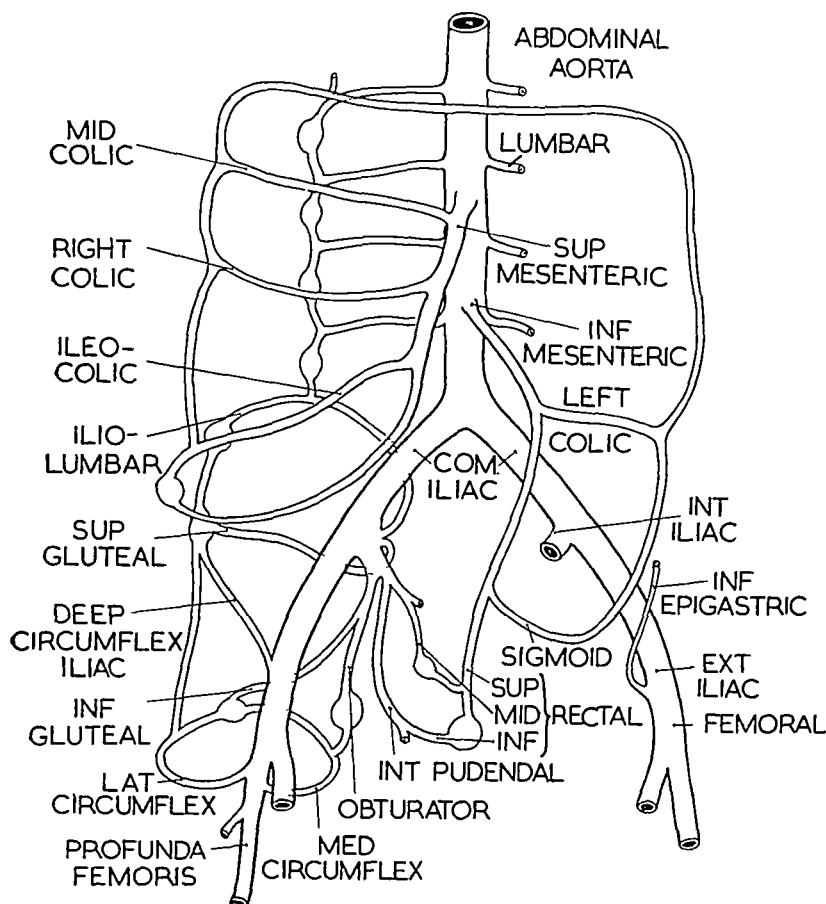


FIG 4—Somatic and visceral anastomoses between abdominal aorta and arteries of lower extremity (Modified from Quiring, D P (1949), *Collateral Circulation* London Henry Kimpton)

provide an insufficient source of nourishment to the legs, and indeed at best it is precarious But if the aortic block is slowly produced it is enough for the life of the limb, in such cases the greatly enlarged inferior epigastric artery may pulsate so strongly that it may be mistaken for the femoral

PART II—AORTIC THROMBOSIS

In these cases the diagnosis is not so certain as in our cases of aortic embolism, but we have observed 11 patients aged from 35 to 57 years

in whom the diagnosis was probably thrombosis of the abdominal aorta. In at least one case it is likely that the initial episode was embolic, but at our first examination none of the patients told the dramatic story of acute occlusion of the aortic bifurcation. There were 10 males and one female (Table I)

TABLE I
Aortic Thrombosis Details of Cases

Case	Sex	Age	Type of Onset	Presenting Symptoms	Duration
1	M	44	Gradual	Claudication in calves at 50 yds Cold feet	3 years
2	M	47	Gradual	Claudication in calves and thighs at 100 yds Cold feet	2 years
3	M	50	Gradual	Claudication in calves at 80 yds	7 years
4	M	50	Gradual	Right leg amputation 7 years Left leg amputation 5 years Gangrene right stump 3 months	7 years
5	M	50	Gradual	Claudication in calves at 20 yds Cold and numb feet Uselessness of legs	1 year
6	M	56	Gradual	Claudication in calves at 50 yds Rest pain	4 years
7	M	57	Gradual	Swelling of ankles Claudication in calves at 20 yds Night cramps in legs	11 years
8	M	52	Acute on chronic	Cold feet Claudication in calves at 50 yds Night cramps in legs Numbness and loss of power in legs	2 years and 2½ months
9	M	57	Acute on chronic	Swelling of legs Pain in lumbar region Claudication in left leg at ½ mile	1 year and
10	M	35	Episodic	Loss of power, coldness and pain in right leg Claudication in calves at 20 yds Cold feet	6 months 8 months
11	F	57	Sudden	Loss of sensation in feet Burning in feet at night Loss of power in right leg Claudication in calves and thighs at 20 yds Night cramps in legs Cold feet	1 month

Clinical Observations

(a) THE ONSET

In 7 patients the onset was gradual. When first seen, 5 of this group had symptoms suggestive of aortic occlusion. None was seen less than one year from the onset of symptoms and in one patient symptoms had been present for eleven years. In these cases there was a history of claudication beginning in one or both calves, and of progressive shortening of the "claudication distance". The other 2 patients in this group (Cases 3 and 4) had been under observation for seven years, during this period symptoms of arterial occlusion in one leg were followed by similar symptoms in the other leg and later by signs of a proximal extension of the thrombotic process. In Case 4

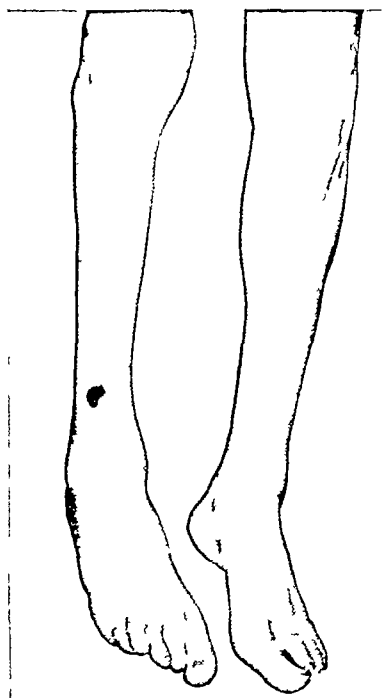


FIG 6—Aortic thrombosis CASE 9—
To show extreme wasting of right
leg which was paralysed

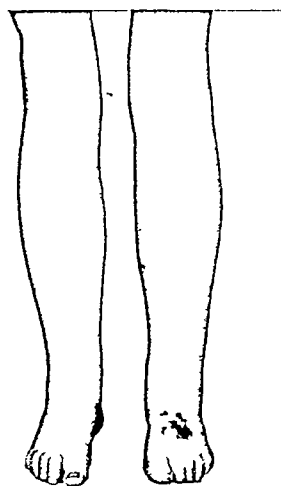


FIG 5—Aortic thrombosis CASE 8
—To show swelling of legs and
minor nutritional changes

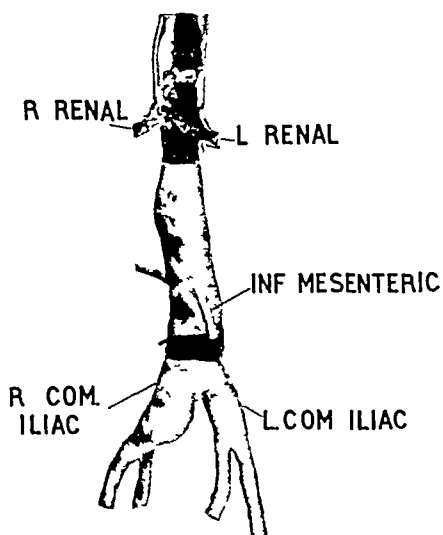


FIG 21—Aortic thrombosis CASE 8—To
show extent of thrombus

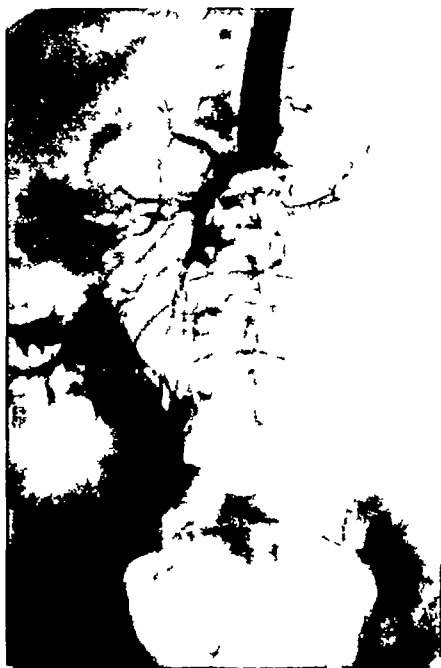


FIG 13—Aortic thrombosis CASE 1—Post
mortem aortogram to show upper level of
thrombus and lack of continuity between
renal arteries and aortic lumen

the aortic occlusion was not complete but the case has been included to illustrate its gradual development

Two patients (Cases 8 and 9) had experienced claudication in the calves for months or years when their symptoms suddenly became more severe. The first patient, who had had claudication in both calves for two years, awoke to find both feet white and numb, and was unable to move his toes. When he hung his legs over the edge of the bed, the feet became red, to the accompaniment of intense paræsthesiæ. Later he was able to walk and to work, but when he went to bed his feet again blanched, he lost the power to move his toes and had to sleep sitting in a chair. The second patient had been unable to work for six months because of backache and pain in the left calf on exercise. Within a subsequent period of two months, he had two episodes of sudden loss of power in the right foot associated with numbness of the toes and cramp in the calf. After the second of these incidents the right foot remained persistently cold and painful. These 2 cases fall into the group of "acute on chronic occlusion."

In Case 10 the onset was episodic. The patient, who suffered from subacute bacterial endocarditis, related two separate incidents in which he had sudden pain, first in the left then in the right leg. When he recovered from the endocarditis he found that he was unable to walk more than 20 yards without experiencing pain in both calves, and he noticed that his feet were always cold. It would appear that two separate embolic episodes were followed by consecutive proximal thrombosis which reached the aortic bifurcation.

Only one patient (Case 11) had a sudden onset. One evening while out of doors she felt "all the feeling going out of her right leg." She had great difficulty in walking, had to drag her legs along and was unable to board a tram-car without assistance. Subsequently she had claudication in both calves, cramp in both legs at rest in bed, and she complained of cold feet. On examination one month after the onset there was no evident source of embolism.

(b) COMPLAINTS

The most constant complaint was intermittent claudication in the calves. It was experienced by all patients and by the time they had come under our care their "claudication distances" on level ground were very short, the longest was 100 yards, the shortest (4 cases) 20 yards. Two patients had claudication pain in the muscles of the buttock also, in the territory of the internal iliac artery. The next most common symptom was persistent coldness of the feet, of which 7 patients complained. Three patients complained of cramp in the legs at rest in bed, severe enough either to prevent sleep or to waken the patient after he had gone to sleep, in 2 of the 3 patients the cramps were associated with a feeling of numbness and loss of power in the limbs and they were relieved if the patient got up and walked about. Subjective disturbances of sensation in the feet were noted by 5 patients. These included a

feeling of numbness, chiefly in the soles, a sensation of "burning" at rest in bed and severe rest pain. Four patients remarked upon loss of power, weakness or "uselessness" of their lower limbs. Swelling of the legs and feet was noted in 2 cases.

(c) CLINICAL FEATURES

(i) *Those Directly Related to the Aortic Thrombosis*—Absence of pulses in the lower limbs was the most constant and most important finding. In 8 cases pulsation could not be felt in the femoral arteries or in any of the more distal vessels. In Case 1 weak femoral pulses were

TABLE II
Aortic Thrombosis Pulses

Case	Aorta	External Iliac		Femoral *		Additional Pulses
		R	L	R	L	
1	Pulsation in upper epigastrium becoming faint above umbilicus	?	±	?	±	None
2	Present	—	—	—	—	None
3	Pulsation felt high in abdomen, not lower	—	—	—	—	Left circumflex iliac
4	Present	—	+	—	+	None
5	Felt to 0.5 cm below navel only	—	—	—	—	None
6	N R	N R	N R	—	—	N R
7	Pulsation stopped 3 cm above umbilicus	—	—	—	—	None
8	N R	?	?	—	—	None
9	Pulsation stopped 2-3 cm above umbilicus	—	—	—	—	None
10	Obese Pulse not felt	—	+	—	±	None
11	Pulsation stopped 2 cm above umbilicus	—	—	—	—	None

N R = No record ? = Doubtful pulse ± = Weak or faint pulse
+ = Normal pulse — = Absent pulse

* Pulsation was absent distal to the femoral arteries in all cases.

felt and in Cases 4 and 10 a feeble pulse could be felt in the left femoral artery only *. Data regarding pulsation in the abdominal aorta and iliac vessels are presented in Table II.

In addition to absence of pulses, other signs of vascular insufficiency were present (Table III). The feet were cold to the touch. In one case (Case 5) pallor of the feet was present even when the patient stood erect. In all cases in which the effect of raising and lowering the feet was tested, marked pallor on elevation and either cyanosis or rubor on dependency were recorded. Four patients had œdema of one or both legs, in one of these there was gross swelling of the feet and legs and blistering of the skin of the feet (Fig. 5). In 8 cases the nutrition of the

* In Case 10 after lumbar sympathectomy the amplitude of this pulse was improved.

TABLE III

Aortic Thrombosis Vascular Disturbances in Lower Limbs

Case	Temperature of Feet	Skin Colour of Feet			Edema	Nutrition
		Horizontal	Elevated	Pendent		
1	Cold	Cyanosed	Pallor	Rubor rt ++ lt +	None	Good
2	Cool	Normal	Gross pallor	Rubor +	None	Good
3	Warm	Rubor	Moderate pallor	Rubor +++	None	Good
4	Both lower limbs amputated					Gangrene rt stump
5	Cold	Pallor	Pallor	Rubor +	None	Fair
6	N R	N R	N R	N R	+	No gangrene
7	Cold	Pink	Pallor	Rubor +	None	Fair
8	Cool	Pale	Pallor	Cyanosed +	+++	Blisters
9	Rt cold Lt warm	Rt rubor Lt pink	Pallor rt ++ lt +	Rubor rt +++ lt +	Rt + Lt none	Gangrene of rt heel and leg
10	Cold	Cyanosed	Pallor	Rubor rt + lt ±	Rt + Lt ++	Good
11	Cold	N R	N R	N R	None	Good

TABLE IV

Aortic Thrombosis Neurological Disturbances in the Lower Limbs

Case	Wasting	Fasciculation	Power	Reflexes *	Sensation
1	+E D B	Present	Good	K J's ++ A J's ±± Plantars ↓↓	Hypæsthesia and hypalgesia of toes
2	General	Present	Normal	All normal	Normal
3	None	Present on rt	Good	All normal	Normal
4	Both lower limbs amputated				
5	N R	N R	Normal apart from E D B on rt = o	All normal	Lt "sock" loss Rt "carpet slipper" loss
6	N R	N R	N R	N R	N R
7	+E D B	Ant and post tibial groups rt and lt	Good	All normal	Normal
8	None	None	Good	K J's ++ A J's -- Plantars ↓↓	Hyperpathia of soles †
9	Rt thigh + Rt leg +++	Present lt calf	Gross weakness below rt knee	K J's ++ A J's -- Plantars o ↓	Rt sciatic loss
10	N R	None	Weakness below knees	K J's ++ A J's -- Plantars ??	Bilateral "stocking" loss
11	None	Ant and post tibial groups rt and lt	Good	All normal	No loss

N R = No record

E D B = Extensor digitorum brevis

* Reflexes are given for right and left legs respectively

Knee and Ankle jerks — + = Normal reflex ± = Diminished reflex — = Absent reflex

Plantars — ↓ = Flexor response o = No response ? = Doubtful response

† In this case elevation of the feet produced an area of sensory loss over the fore feet which recovered when the feet were returned to the horizontal (see Fig 7)

feet was good, only minimal changes in the nails and in the texture of the skin and some atrophy of the pulp of the toes being present. Three patients showed gangrene or pre-gangrenous lesions. One (Case 4) who had had both legs amputated because of gangrene seven and five years before, was re-admitted with patchy gangrene of the right stump. The second (Case 8) was the patient who had gross swelling of the feet, in whom the blistered areas of skin later formed necrotic sloughs, in the third (Case 9) there were patches of gangrene on the right heel and on the front of the right leg (Fig. 6).

In most of the cases neurological disturbances of varying severity were present (Table IV). Generalised wasting of the muscles of the lower limbs and fasciculation in the muscles of the thigh, calf, anterior tibial group and small muscles of the foot were often noted. One patient (Case 10) had weakness of the muscles below both knees, thought

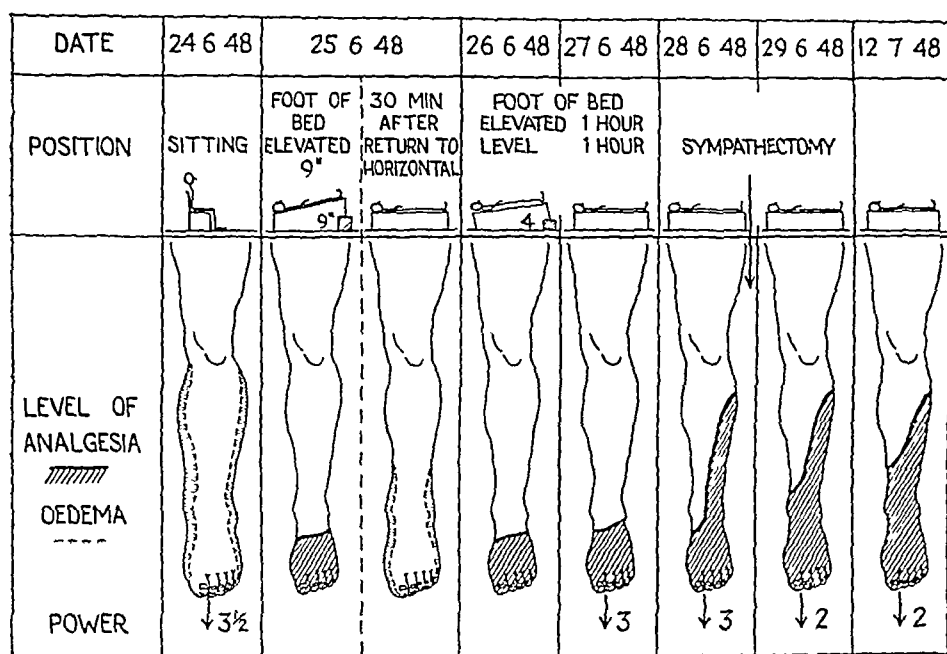


FIG. 7—Aortic thrombosis. CASE 8—To show variations in swelling and sensory level in various positions and at different dates
(Full power of flexion of foot = 5)

to be hysterical. In 2 patients (Cases 8 and 10) both ankle jerks were absent and, in a third case (Case 1) they were diminished. Five patients had some loss of sensation. The patient (Case 10) who was thought to have hysterical weakness of the muscles of the legs had "stocking" areas of analgesia. Another patient (Case 5) had an area of anæsthesia over the foot and lower third of the leg on both sides, and analgesia of the distal parts of both feet. One patient (Case 1) had hypæsthesia and hypalgæsia of the toes only. In Case 8 when the patient was horizontal only slight hyperpathia of the soles was noted, but when the feet were elevated by raising the foot of the bed on 9-in. blocks, in an effort to reduce oedema, they blanched and overnight an area of anæsthesia

and analgesia became detectable (Fig 7), this quickly disappeared when the blocks were removed

Neurological signs were most prominent in Case 9. This patient had a right drop-foot with contractures of the muscles of the calf and of the long extensors of the toes. The muscles below the right knee were grossly wasted and fibrotic, the peronæi were paralysed and the other

TABLE V

Aortic Thrombosis Cardiovascular System

Case	Blood Pressure	Heart	Arteries	Urine
1	144/ 84	Clinically—soft mitral systolic murmur E C G —inversion of T 3 Pathol —coronary atheroma	Calcified external iliac arteries	N A D
2	200/110	Clinically—angina of effort —aortic systolic murmur E C G —myocardial damage	Occlusive vascular disease rt arm Calcified vessels in thighs	N A D
3	130/ 80	Clinically—normal E C G —normal		N A D
4	Max 146/60 Min 112/50	Clinically—normal E C G —coronary ischæmia Pathol —myocardial infarction	Calcified thoracic and abdominal aorta Occlusive vascular disease rt arm	N A D
5	200/110	Clinically—mitral systolic murmur Pathol —slight hypertrophy and dilatation only	Nicking of retinal veins	N A D
6	Max 180/105 * Min 125/ 80 *	Clinically—enlarged heart —congestive failure E C G —no definite abnormality Pathol —hypertrophy and dilatation	Narrowing of retinal arteries	Slight pyuria only
7	170/ 80	Clinically—N A D E C G —normal	Calcification in dorsalis pedis artery	N A D
8	150/ 92	Clinically—N A D Pathol —myocardial infarct —coronary atheroma		N A D
9	150/ 90	Clinically—mitral systolic murmur E C G —within normal limits	Calcified and dilated abdominal aorta	N A D
10	115/ 76	Clinically—mitral stenosis —aortic incompetence E C G —normal		Trace of albumin
11	174/110	Clinically—normal E C G —normal	"Silver wiring" of retinal arteries Calcified aorta and iliac arteries	N A D

* Observations made over a period of 14 weeks

muscles of the leg showed only feeble voluntary power. The area of sensory loss corresponded to the distribution of the right sciatic nerve. We believe that such neurological findings are exceptional, and that they were the result of embolic occlusion of the right popliteal artery *

(11) *Those Indicating Generalised Cardiovascular Disease*—The majority of the patients had definite evidence of general disease of the

* Later the limb was amputated and dissected, the femoral artery was patent but the popliteal artery was occluded by an embolus, infarcts were present in tibialis anterior and peronæus longus

cardiovascular system (Table V) The blood pressure was elevated in 4 cases, was at the upper limit of normal in 3 cases and could be regarded as normal in only 4 cases In 3 patients there was clinical evidence of heart disease In Case 2 there was angina on effort, a loud aortic systolic murmur and electrocardiographic evidence of myocardial damage, in Case 6 there had been several episodes of congestive cardiac failure, the cause of which was undetermined, in Case 10 there had been an attack of subacute bacterial endocarditis superimposed on mitral stenosis and aortic incompetence In Cases 4 and 8 the heart was considered to be normal on clinical examination, later both patients died from cardiac failure, at autopsy myocardial infarction and advanced atheroma of the coronary arteries were found In Case 1 also autopsy disclosed unsuspected coronary atheroma In Cases 2 and 4 there was evidence of occlusive vascular disease affecting the right upper limb, shown in Case 2 by claudication in the biceps muscle, absence of the brachial pulse and a feeble radial pulse In Case 4 pulsation was absent in the distal third of the right brachial artery but good pulsation was felt in the profunda and ulnar collateral arteries, at the wrist the ulnar pulse was present, the radial absent In 2 patients (Cases 7 and 11) arteriosclerosis of the retinal vessels was present

(d) SPECIAL INVESTIGATIONS

(1) *Circulation in the Lower Limbs*—Oscillometric readings of pulsation at the ankle were attempted in 6 cases, with the instrument used, the normal reading varied from 1.5 to 4 units In the cases of aortic thrombosis the maximum recorded was 0.75 units (at the right ankle in Case 5) and in 2 cases oscillations were absent In Case 9 the cuff of the oscillometer was applied to the thighs, even at this level the maximum reading was 0.6 units In 5 patients (Cases 1, 3, 7, 9 and 10) vasodilatation tests were performed (Table VI) It will be noted that in 4 of these the skin temperature of the toes did not reach 30°C and the blood flow through the feet was below normal levels In Case 3 the feet remained persistently warm (32.5°C) although the maximum blood flow was low In Case 10 before sympathectomy a recording of blood flow in the feet could be obtained only when the collecting cuff pressure was considerably less than the diastolic pressure in the arms, an indication that arterial pressure in the legs was low (Fig. 8)

The response to exercise was investigated in 5 cases (Cases 1, 2, 7, 9 and 10) None of the patients was able to perform a standard exercise test—plantar flexion of the foot against a weight of 6 lb at a rate of 100 excursions in two minutes In 4 cases the resting blood flow in the legs was low, and although attempts were made to obtain records after such mild exercise as the patients were able to perform, the records were unsatisfactory The response to exercise was undoubtedly poor in all cases In Case 2 a substitute test was used,

"walking on the spot" for one minute. Before exercise the blood flow through the leg was low and the tracing did not show pulsation (Fig 9). During exercise the patient complained of pain in the calves and the feet blanched. After exercise the pain and the pallor continued for two minutes. During the first minute after exercise the blood flow

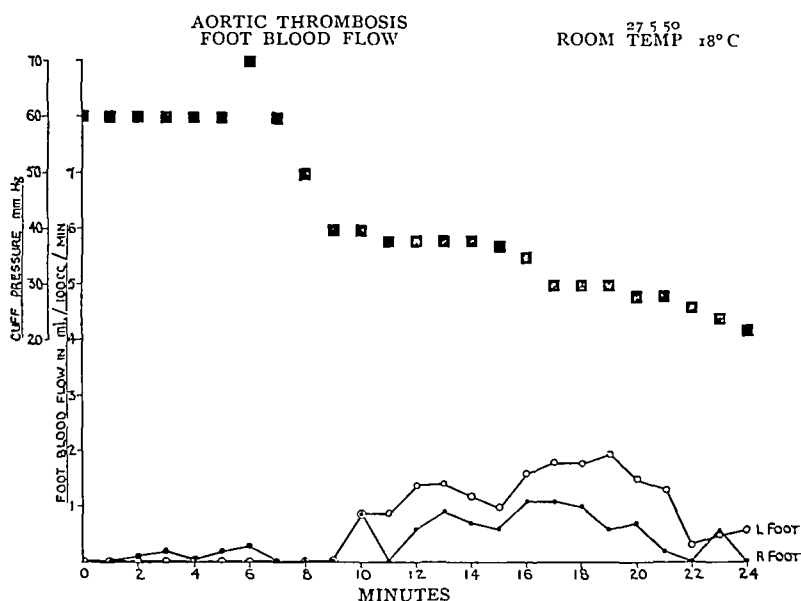


FIG 8—Aortic thrombosis CASE 10—To show variations in foot blood flow at different pressures of occlusion cuff

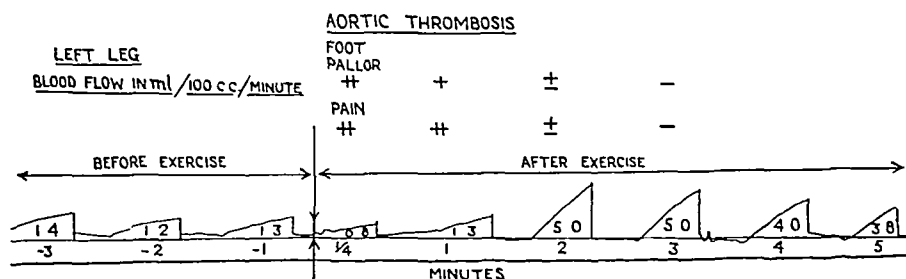


FIG 9—Aortic thrombosis CASE 2—To show flow of blood in one leg before and after exercise

in the leg was low, it rose to a maximum at two minutes and thereafter slowly returned to the resting level (Fig 10). This finding is similar to that recorded by Shepherd (1950) in patients suffering from occlusive vascular disease who have severe intermittent claudication.

(ii) *Aortography*—In 5 cases attempts were made to visualise the obstruction at the aortic bifurcation by injecting an opaque medium *

* Fifty per cent perabrodil or diadone

into the aorta above the level of the aortic arch. In 4 cases this was done at the same time as lumbar sympathectomy was performed. On the whole, these attempts were not successful. In Cases 1 and 2, pulsation in the aorta could not be felt until just below the diaphragm. The injections were made at this level but only the renal circulation and later the pelvis and calves were outlined. In Case 3, the injection was made into a non-pulsatile portion of the aorta at the level of the second lumbar vertebra; the radiograph showed only a few small vessels in the muscles of the back and abdominal wall. The most satisfactory aortogram was obtained in Case 3 (Fig. 11); pulsation was felt at the aortic

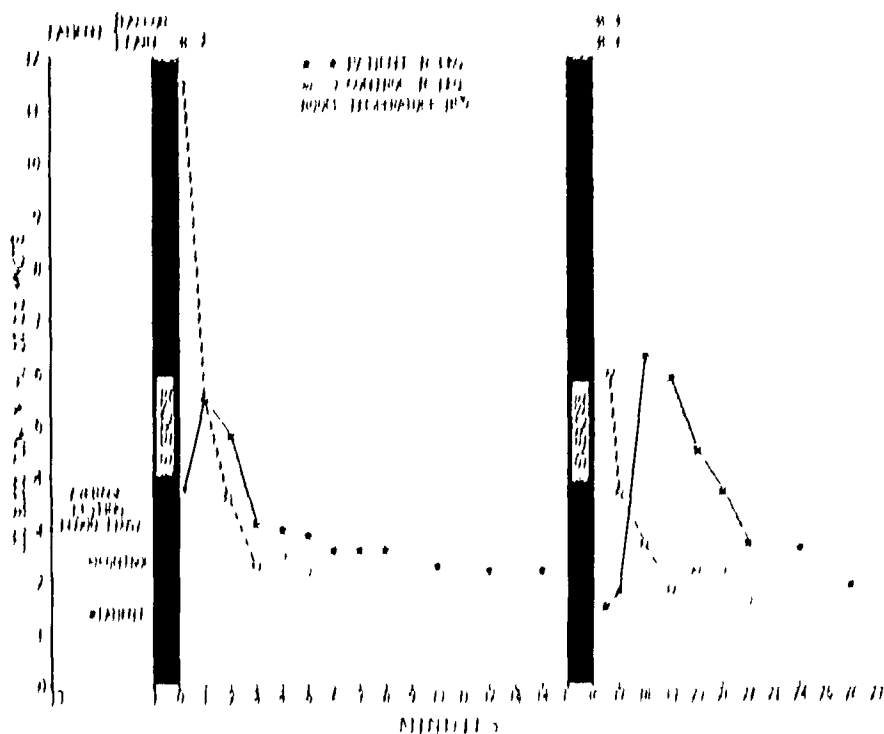


FIG. 10. Aortic thrombosis—Case 1. To show delay in return to resting blood flow after release.

bifurcation and in the right common iliac artery; the aortogram confirmed that the bifurcation and right common iliac artery were patent. The right external iliac artery was completely occluded and there was evidence of a poor collateral circulation in the right side of the pelvis.

(iii) *Myelograms*. Radiological tests for syphilis were done in 3 cases and all were negative. We have no reason for thinking that syphilis could have been an aetiological factor in the other 3 cases.

In 5 cases radiographs of the abdomen and lower limbs revealed calcification in the walls of the larger arteries, in 3 cases calcification was not seen and in the remaining 3 cases radiographs were not taken.

(e) TREATMENT AND PROGRESS

Four patients underwent bilateral lumbar sympathectomy, in 2 cases (Cases 2 and 7) the operations were done in two stages through lumbar incisions, and in 2 (Cases 1 and 10) both chains were dealt

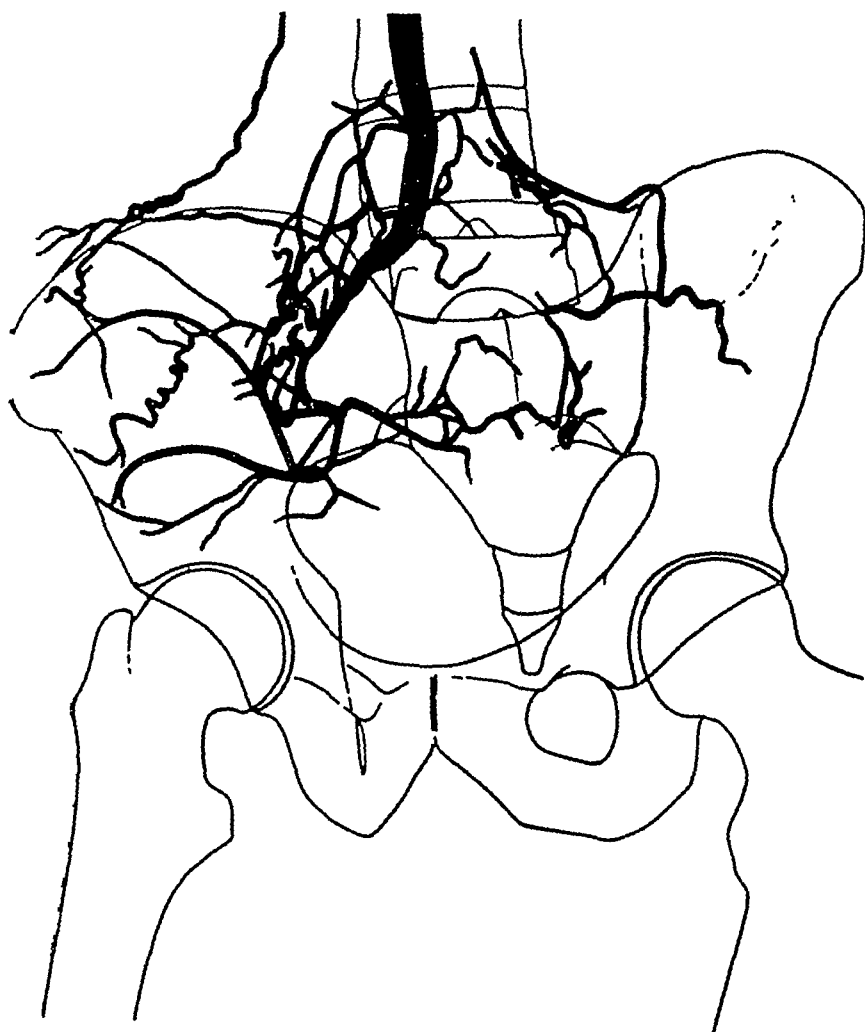


FIG 11 —Aortic thrombosis CASE 5 —Tracing of aortograph to show partial filling of right common iliac artery

with through a transperitoneal approach. Two patients (Cases 5 and 8) had only a left lumbar sympathectomy, both died before the second operation. One patient (Case 11) received two intrathecal injections of alcohol to relieve severe rest pain. One patient (Case 9) had a right supracondylar amputation performed because of gangrene. In Case 4, both legs had been amputated previously because of peripheral arterial occlusion (Fig 12), at a later date signs appeared suggesting proximal

extension of the disease and disarticulation at the right hip had to be performed. The remaining 2 patients (Cases 3 and 6) received no special treatment, in one of these (Case 6) the diagnosis was not made before death.

The results of sympathectomy have been disappointing. Three patients (Cases 1, 5 and 8) died within one month of the operation before any clinical assessment of its effect could be made. In the remaining 3 cases (Cases 2, 7 and 10) there was no good evidence that intermittent claudication, which was the disabling symptom in all 3, was helped

TABLE VI

Aortic Thrombosis Vasmotor Studies

Number	Age	Room Temperature °C	Limb	Before Sympathectomy				After Sympathectomy		
				Toe Temperature °C		Foot Blood Flow ml/100 c.c./min		Time Months	Toe Temperature °C Average Resting	Foot Blood Flow ml/100 c.c./min Average Resting
				Average Resting	Maximum	Average Resting	Maximum			
1	44	18.20	L	26.5	27.0	3.2	3.3	½ and ½	27.0	4.5
			R	27.0	27.8	1.3	1.5		24.0	5.1
2	47	18	L					4 and 11	17.4 *	3.4
			R						24.6	3.2
3	50	21	L	32.5	31.0	3.2	3.0		No sympathectomy	
			R	32.5	32.0	3.4	5.4			
7	57	18.19	L	21.2	25.3			8	30.8	4.9
			R	21.3	24.0				30.2	4.5
9	57	17.5	L	25.5	22.5				No sympathectomy	
			R	21.5	19.0					
10	35	18.20	L	21.8	28.5	1.4		1½		8.7
			R	22.8	28.8	0.9				10.6
Control †	20	17.23	Average of 10	21.7	34.7	3.5	19.6	½ 1½	32.2	8.7
	43		Range	17.1-24.3	33.6-35.0	1.5-7.0	13.0-30.8		28.9-34.5	3.5-18.0

* Reading made two months after another episode of arterial occlusion in left leg. The blood flow record in the next column was made seven months later.

† Average of 10 limbs in 5 cases of acrocyanosis with normal pulses.

by the operation. On the other hand, vasomotor studies on 4 patients (Cases 1, 2, 7 and 10) after sympathectomy indicated that the blood supply to the feet was improved (Table VI).

At the time of writing, 6 patients have died and 5 are alive. The deaths occurred as follows —

CASE 1 — Immediately after sympathectomy his feet were warm and pink, the veins were well filled and the hypæsthesia and hypalgesia of the toes disappeared. One week after operation he began to cough and brought up considerable quantities of sputum, albuminuria was noted and the blood urea began to rise. On the eleventh day the feet were noted to be cold and during the next forty-eight hours the coldness spread proximally to the knees. On the sixteenth post-operative day he died.

CASE 2—This patient was not greatly improved by a high bilateral lumbar sympathectomy. Two months later he had an episode in which further thrombosis in the left lower limb occurred. At best he could walk only 50-60 yards and his activity was restricted not only by the state of his lower limbs but also by angina of effort and exertional dyspnoea. Fifteen months after sympathectomy he died suddenly at home.

CASE 4—The clinical progress of this patient is illustrated in Fig. 12. Following the disarticulation at the right hip on 30.1.51, his condition gradually deteriorated, the operation wound failed to heal, he became grossly oedematous and died five months later from cardiac failure.

DATE	FEBRUARY 1944	MARCH 1946	DEC. 1946-MAR. 1947	JANUARY 1951	JUNE 1951
AGE	43	45	46	50	50½
SYMPTOMS	SUDDEN ONSET OF PAIN IN RT CALF FOLLOWED BY CLAUDICATION PAIN IN RT FOOT	PAIN IN LEFT FOOT AT REST AND ON EXERCISE	PAIN IN LEFT FOOT AT REST AND ON EXERCISE CLAUDICATION IN CALF AT 50 YD	GANGRENE OF RT STUMP PAIN IN RT STUMP	GANGRENE OF RT STUMP
AMPUTATION	2.3.44 TRIMMED 1.3.45		7.1.47 PINCH GRAFTS 27.3.47	DISARTICULATION 30.1.51 EXCISION OF SLOUGH 30.3.51	DIED 28.6.51

FIG. 12—Aortic thrombosis. CASE 4—Life history of patient suffering from aortic thrombosis over a period of seven years.

CASE 5—The patient died forty-eight hours after left lumbar sympathectomy had been performed. The circulation in the left lower limb became worse after the operation and he experienced much pain in this leg. He suddenly became dyspnoeic, collapsed and died. At autopsy right bronchopneumonia and bilateral pulmonary oedema were found.

CASE 6—A diagnosis of aortic thrombosis was made incidentally in a patient who was seriously ill with congestive cardiac failure from which he died.

CASE 8—For four days this patient was treated by elevation of the lower limbs to reduce the oedema. It was found that he would not tolerate high elevation of the feet because pallor and paralysis developed. With moderate elevation, however, the oedema was much reduced but the area of sensory loss increased. Left lumbar sympathectomy was then performed. After the operation the condition of the left lower limb became worse. It was cyanosed and weak, and insensitive below the knee (Fig. 7) and there was considerable residual pain in the leg. Fifteen days after operation he had

a sudden attack of dyspnoea without precordial pain Twelve days later he had an attack of precordial pain and pericardial friction was noted He died one month after operation, the clinical diagnosis being myocardial infarction At autopsy this was confirmed, there was also fibrino-purulent pericarditis, bilateral pleurisy and oedema and congestion of the lungs with infarcts in both lower lobes

Two of the male survivors (Cases 7 and 10) have had bilateral lumbar sympathectomy, the intervals since operation are fourteen months in Case 7 and seventeen months in Case 10 Intermittent claudication is still a serious disability to both patients, neither can walk more than 50 yards The nutrition of their feet remains good although it is eleven years and two years respectively since their initial symptoms Of the remaining male patients, one (Case 9) within a year of the onset of symptoms had his right leg amputated and in the other (Case 3) the diagnosis of aortic thrombosis has been made within recent months, his progress cannot yet be reported

The only female patient in the series (Case 11) had two intrathecal injections of alcohol (one in February 1949 and the second in July 1949) to relieve severe rest pain She is now (June 1951) able to walk distances up to 100 yards and to do her own housework The nutrition of her lower limbs remains good but she suffers from attacks of cramp in the right leg When she was seen in one of these it was noted that blanching of the right foot accompanied the pain, this suggests that vasospasm may contribute to the attacks

Pathological Observations

In 5 of the fatal cases autopsies were performed and the state of the abdominal aorta and main arteries of the lower limbs was determined

CASE 1—The thoracic aorta was injected with 50 per cent perabrodil and a radiograph (Fig 13) showed the conical end of the thrombus just proximal to the origin of the superior mesenteric artery The latter was well filled Both renal arteries and their main branches were clearly outlined but there was no apparent connection between the aorta and the renal arteries The arteries in the pelvis and in the lower limbs were not filled Some of the lower intercostal arteries were outlined but there was no evidence of hypertrophy to suggest that these had formed part of a collateral circulation to the lower limbs

When the aorta was examined it was found that proximally the thrombus extended above the renal arteries to the coeliac axis, the latter artery and the superior mesenteric artery were patent Distally the thrombus extended a few millimetres beyond the origin of the right external iliac artery and 2 cm beyond the origin of the left external iliac artery, both femoral and both popliteal arteries were patent The internal iliac arteries were blocked by old thrombus Beyond their origin from the aorta the lumbar arteries, inferior mesenteric artery and middle sacral artery were patent (Fig 14) The walls of the thoracic aorta and external iliac arteries were noted to be atheromatous but the walls of the femoral arteries and the popliteal arteries were healthy The iliac, femoral and popliteal veins were normal

After the aorta and its branches had been fixed in a state of distension, the specimen was split longitudinally into anterior and posterior halves (Fig 15).

The thrombus in the aorta extended from the bifurcation to the level of the coeliac axis. The proximal end was convex and extended higher posteriorly than anteriorly, thus a funnel-shaped opening leading to the superior

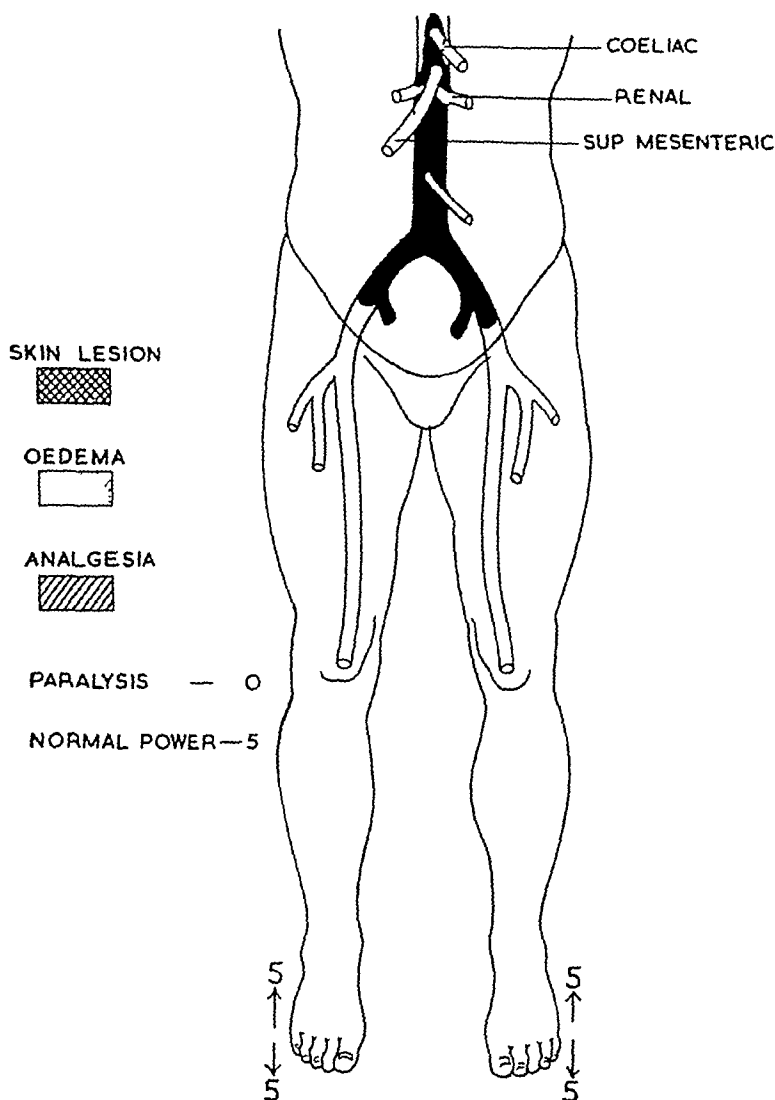


FIG 14 —Aortic thrombosis CASE 1 —To show extent of thrombus and absence of changes in lower extremities (Compare Fig 13)

(Figures above and below arrows indicate power in dorsiflexors and plantar flexors respectively)

mesenteric artery was formed. At the level of the renal arteries an irregular transverse channel lined by smooth clot connected the orifices of the renal arteries. This channel communicated posteriorly with one or both of the second lumbar arteries. The clot surrounding the channel appeared to be of more recent origin than the remainder of the thrombus.

When these findings are correlated with the curious appearance in the

post-mortem aortograph (Fig 13) in which connections between the aorta and the renal arteries seemed to be absent, they suggest that the renal arteries were filled only during systole by way of a narrow channel between the thrombus and the wall of the aorta, during diastole the aortic wall would

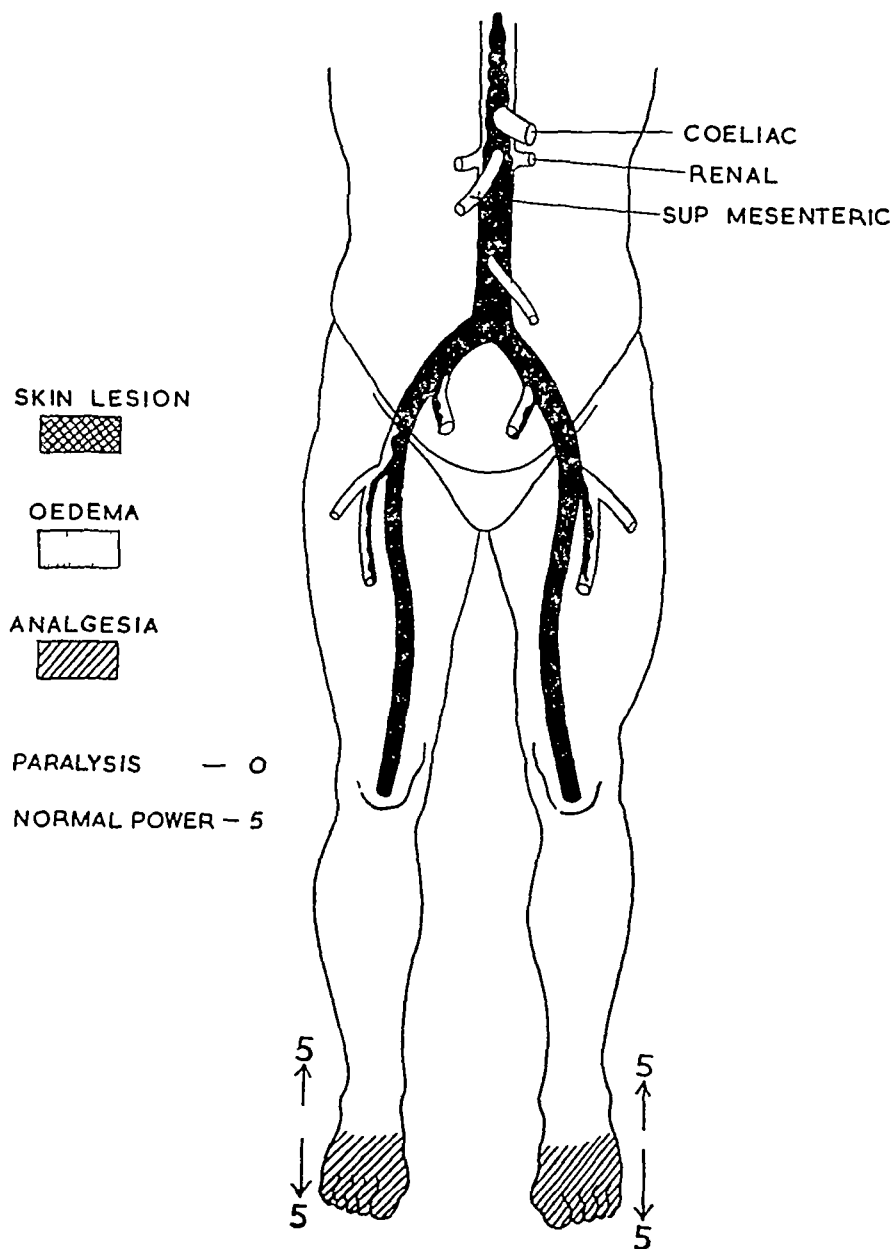


FIG 19—Aortic thrombosis CASE 5—To show extent of thrombus and minimal changes in lower extremities

lie against the thrombus (Fig 16)

CASE 4—The abdominal aorta was partially occluded by red adherent thrombus from a point 2 cm distal to the renal arteries to its bifurcation. The somewhat sinuous but smooth-walled channel through this clot lay chiefly to the left and communicated with the left common iliac artery which was patent (Fig 17). On the right, the origin of the common iliac, this vessel

itself and its terminal branches were completely occluded by organised clot. The coeliac, superior mesenteric and renal arteries were patent. The inferior mesenteric artery, although blocked at its origin by the aortic clot, was itself patent. Gross calcification was present in the walls of the thoracic and

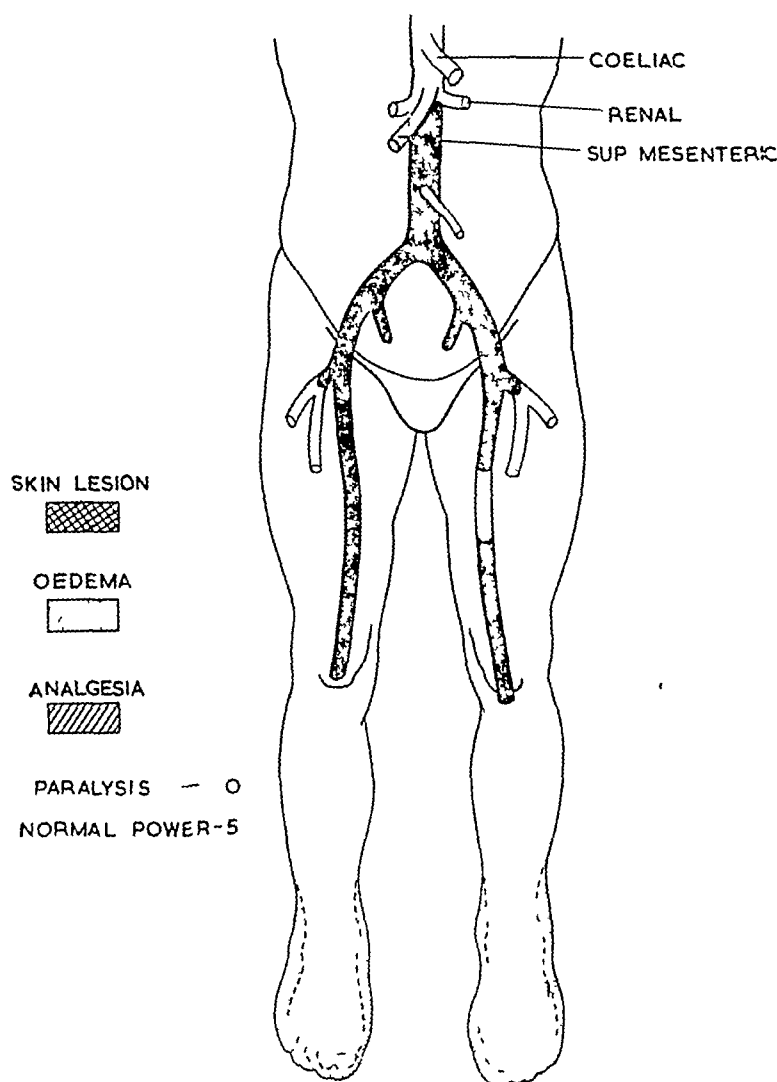


FIG 20 —Aortic thrombosis CASE 6 —To show extent of thrombus and changes in lower extremities
(No record of power)

abdominal aorta, the coeliac, superior mesenteric and iliac arteries

CASE 5 —The proximal end of the thrombus in this case extended 2 cm above the origin of the coeliac artery. At this level the block was incomplete and the thrombus was adherent to the postero-lateral wall of the aorta, the block became complete below the renal arteries (Fig 18). The renal arteries, superior mesenteric artery and coeliac axis were patent. The common iliac

arteries were both completely occluded (Fig 19) and on both sides thrombus was continuous as far distally as the popliteal arteries. Calcification was present in the walls of both common iliac arteries.

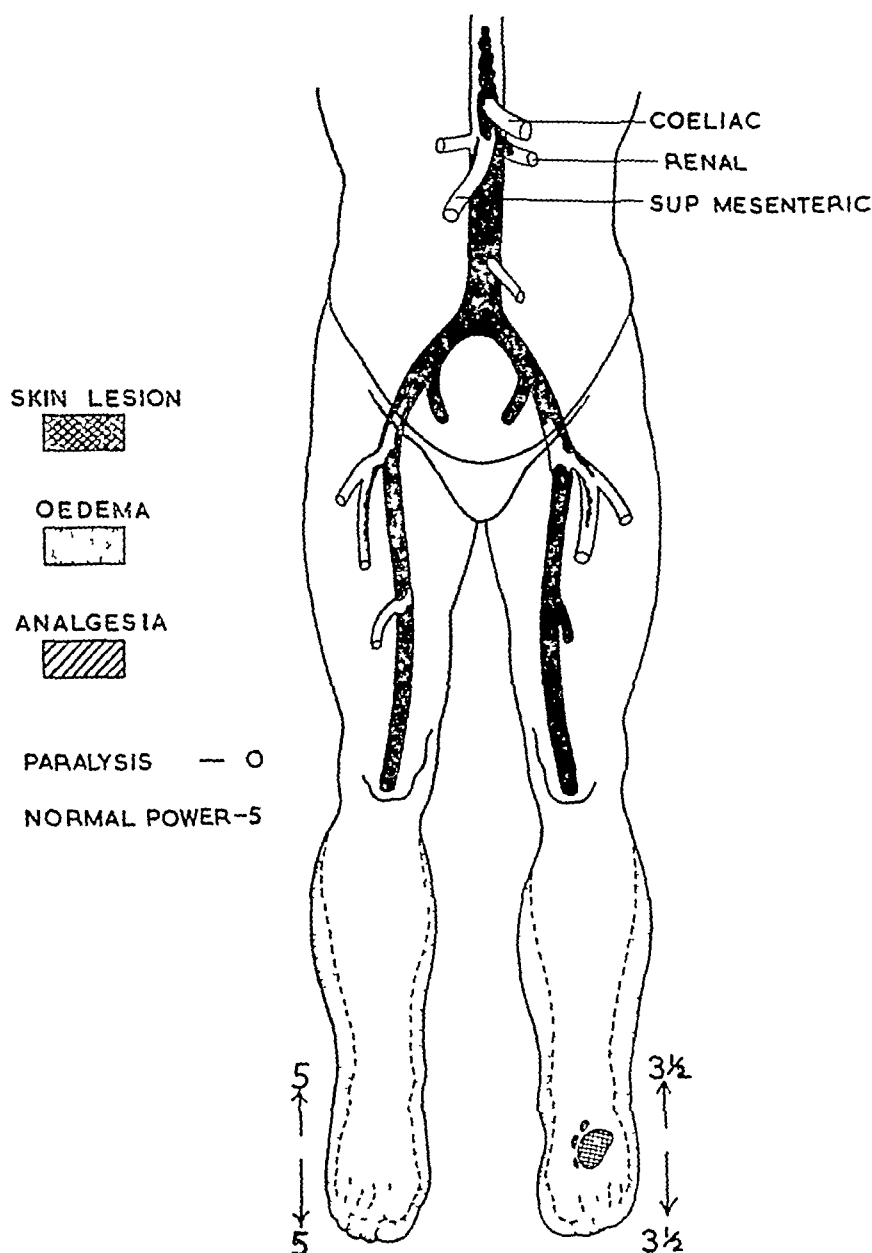


FIG 22 —Aortic thrombosis CASE 8 —To show extent of thrombus and changes in lower extremities

CASE 6 —The aorta was completely blocked to the level of the renal arteries which were patent. The arteries of the lower limbs were occluded from the popliteals proximally, on the right the occlusion was continuous through the femoral and iliac vessels to the aortic bifurcation, but on the left a segment of the femoral artery in Hunter's canal was free from thrombus (Fig 20). Only

the upper portion of the thrombus was recent, the remainder was pale, reddish-brown thrombus of considerable age. The vessel walls showed only a slight degree of calcification.

CASE 8—In this case the thrombus extended above the celiac axis but at that level did not completely occlude the aortic lumen. The celiac and superior mesenteric arteries were patent. There was an old organised thrombus on the right side of the aorta which was not filling the entire lumen and had not occluded the right renal artery (Fig. 21). Over this lay more recent red friable thrombus which had completed the occlusion of both aorta and left renal artery. This must have formed subsequent to the aortograph made four weeks before death (Fig. 11). Both common iliac arteries and the femoral and popliteal arteries were occluded (Fig. 22).

DISCUSSION

Only within the last ten years has it been recognised that thrombosis of the aorta can occur insidiously and present a clinical picture which does not suggest a vascular catastrophe. Leriche (1940) first described the syndrome and discussed its treatment by lumbar sympathectomy and resection of the aortic bifurcation. In subsequent publications (Leriche, 1946, Leriche and Morel, 1948) he has amplified his views on the subject and reported further examples. Since Leriche's original description, a number of continental (*e.g.* Morel, 1943, Martorell, 1946) and American (*e.g.* Holden, 1946, Price and Wagner, 1947, Ortner and Griswold, 1950) writers have recognised the syndrome and have reported cases, but the condition has not yet been discussed in British medical literature.*

This insidious type of aortic thrombosis is not a rare condition, within a period of twenty months, Elkin and Cooper (1949) saw 10 cases and Milanes *et al* (1950) have recently reported a series of 13 cases. Statistics compiled from autopsy material, in which it was often difficult to separate cases of embolism from cases of thrombosis of the aorta, tended to suggest that aortic thrombosis occurred more often in women than in men (Hesse, 1921, Rothstein, 1935, Reich, 1943). Since the recognition of the clinical picture of the insidious type, it has become apparent that like other forms of occlusive vascular disease aortic thrombosis occurs predominantly in males. Indeed the female patient reported in the present series is only the fourth† in the literature since 1940, Delannoy (1945) described the condition in a woman of 41 and Milanes *et al* (1950) have two females in their series. The condition is not essentially a senile one. It occurs most often in the fifth and sixth decades but has been reported in patients as young as 29 years and as old as 69 years. The features originally described by Leriche were—In the male, inability to maintain a stable

* Since this paper went to press, Goodwin, J. G., and Petric, E. (1951), *Brit Heart Journ*, 13, 554, have described a case and discussed the condition.

† A fifth female patient was reported by Straus *et al* (1946) but in this case the aortic thrombosis was more acute and was probably related to a course of radiotherapy given for a supposed carcinoma of the cervix and to subsequent pelvic sepsis.

erection because of reduced blood flow through the internal pudendal arteries, extreme fatiguability of the lower limbs, global atrophy of the lower limbs, absence of nutritional changes in the skin and nails, and pallor of the feet even when the patient was standing

None of our male patients complained spontaneously of the first of these symptoms and on systematic enquiry not all admitted impotence. Elkin and Cooper (1949) found that only five of their 10 patients were unable to maintain a stable erection. Impotence may not occur in those cases in which the internal pudendal artery is refilled through collateral channels. Leriche stressed that the difficulty with the lower limbs was not true intermittent claudication, but extreme tiredness coming on rapidly when the patient walked and sometimes occurring even when he was standing. In our cases the presenting complaint appeared to be typical intermittent claudication in the muscles of the calf of the leg appearing after very short distances. The pain seemed to take longer (up to ten minutes) to pass off than in cases of intermittent claudication caused by obstruction of the femoral or popliteal artery. The patients were always aware that both legs were affected, whereas the patient who has separate episodes of occlusion affecting first one popliteal or femoral artery and then the other will usually state that the pain affects only the more recently affected limb. If the source is not an osteo-arthritic hip joint, complaint of pain on exertion in the muscles of the buttock or thigh should always raise the suspicion of high vascular occlusion. Intermittent claudication in the gluteal muscles is an important symptom because it indicates that the internal iliac artery is occluded.

Of the other symptoms noted in our cases, coldness of the feet cannot be considered of diagnostic value. It is a complaint of all patients who have occlusive arterial disease and of many who have not. The occurrence of cramps in the legs at night associated in some cases with pallor of the feet and paralysis has not so far as we are aware been previously described in cases of aortic thrombosis. Presumably these symptoms are due to the low blood pressure in the collateral vessels supplying the lower limbs. When the patient lies down, the head of pressure is no longer sufficient to maintain the already precarious blood supply, warning symptoms appear which are relieved when he rises and walks about. Paræsthesiæ, numbness, pain and other subjective sensory disturbances are due to ischæmic neuritis, it is surprising that the typical pains of ischæmic neuritis described by Goldsmith and Brown (1935) have so seldom been noted in cases of aortic thrombosis. Only one of our patients (Case 8) had pain of this nature but the ischæmic neuritis was unilateral and probably due to the previous lodgement of an embolus in the popliteal artery.

The most important sign is the absence of pulsation in the arteries of the lower limbs, especially in the femoral arteries. In any patient who complains of pain in or fatiguability of the lower limbs, even if

the appearance of the limbs does not suggest that the symptoms are of vascular origin, the femoral pulses should always be palpated. Often it is difficult to be certain whether pulsation is present in the popliteal and pedal arteries, but normally the femoral pulse is so strong that unless the patient is very obese inability to feel it indicates a definite vascular lesion. If coarctation of the aorta can be excluded and the patient's symptoms are not of sudden onset, then insidious thrombosis of the abdominal aorta is the most likely diagnosis. Bilateral occlusion of the common or external iliac arteries will produce a similar clinical picture, but can be excluded either by aortography or by inspection of the vessels at operation.

The other vascular disturbances are often minimal and have to be sought carefully. Pallor of the feet when the patient is standing was noted in only one of our cases, but undue influence of gravity on the circulation to the feet as shown by marked pallor on elevation and either rubor or cyanosis on dependency was a constant finding in those cases in which it was looked for. In the early stages the nutrition of the feet is good and it may remain so for many years. Swelling of the limbs was noted in four patients but was probably not directly related to the aortic thrombosis. In one (Case 6) it was undoubtedly due to oedema from cardiac failure, and in another (Case 10) early cardiac failure was suspected. The third and fourth patients (Cases 8 and 9) had gross swelling of the lower limbs which was attributed to postural oedema. For three months the third patient (Case 8) had been sitting in a chair both by day and by night. Two of our cases had superficial gangrene, but in both local factors were responsible for the lesions. Both Leriche (1946) and Martorell (1946) state that unless the patient dies from some other cause, gangrene of the feet eventually develops.

The neurological disturbances can be attributed to the effects of the reduced blood supply upon the nerves and muscles of the lower limbs. Wasting of the muscles is often difficult to detect since it is bilateral and symmetrical and therefore a normal limb is not available for comparison. Fascicular twitching is often observed in the muscles of the lower limbs, not only in cases of aortic thrombosis, but in cases where the occlusion is in the popliteal or femoral artery. The cause of this fasciculation is uncertain. It is coarser than the true fibrillation seen in denervated muscles and resembles the coarse local tetanic fasciculation described by Denny-Brown and Pennybacker (1938). This occurs in fatigue and when there is excessive loss of sodium chloride, and it is closely related to muscle cramp. A muscle fasciculus is a vascular and not a neurological unit, and it is therefore not altogether surprising that circulatory disturbances should lead to abnormal fascicular activity.

Objective disturbances of sensation are the result of ischaemic neuropathy.

An elevated blood pressure in the upper limbs has been noted in

the majority of the reported cases. It is uncertain whether this hypertension is to be regarded as part of the general cardiovascular disease which is present in most cases or whether it is a specific finding related to the aortic thrombosis. Straus *et al* (1946) have attributed it to renal ischæmia as a result of occlusion of the renal arteries, but hypertension is present in many cases in which the thrombus has not extended as high as the renal arteries. When first seen, one of our patients (Case 5) had a blood pressure of 120/70 mm Hg, but three weeks later it had risen to 200/110 mm Hg, in this case the renal arteries were not occluded.

In most cases the occlusion can be attributed to arteriosclerosis. Radiographs of the pelvis and thighs may show that there is calcification in the walls of the large arteries. Our clinical and pathological studies lead us to the conclusion that in some cases thrombosis begins in the vessels of the lower limbs and extends slowly upwards (Cases 3 and 4), whereas in other cases the initial occlusion occurs in the iliac arteries or in the aorta itself. In the latter group the main arteries distal to the block remain patent and could be refilled through collateral channels. Although the clinical features suggest complete occlusion, in some cases aortography may show that the block is incomplete on one side. This was noted in one of our cases (Case 8) and in two of the cases reported by Milanes *et al* (1950). The danger of an incomplete occlusion becoming complete is great, as is shown by the course of events in our Case 8 and by the appearance of the clot in Case 5 (Fig 18). When the occlusion of the aortic bifurcation is incomplete, portions of the thrombus may become detached and lodge in distal arteries, as happened in our Case 9.

Although patients with aortic thrombosis may be severely disabled by intermittent claudication, in many cases the prognosis is surprisingly good both for life and for preservation of the lower limbs. One of our patients has probably had the condition for eleven years, and other instances of long survival have been reported. Death is due either to a sudden extension of the thrombus with involvement of the renal or mesenteric arteries, or to a cardiovascular catastrophe such as myocardial infarction.

Two types of surgical treatment have been advocated: resection of the aortic bifurcation combined with low lumbar sympathectomy (Leriche, 1940), and high bilateral lumbar sympathectomy (Leriche and Morel, 1948). We have no experience of the first of these methods, although a number of successful cases have been recorded. It depends for its success upon early recognition of the condition, and a relatively healthy aorta and iliac arteries. When performed in the early stages, high bilateral lumbar sympathectomy may improve the collateral circulation to the lower limbs. In more advanced cases, even when done in two stages, this operation is not without risk because it may be followed by a rapid deterioration in the circulation in the ipsilateral limb, as happened in two of our cases. Moreover, sympathectomy

does nothing to minimise the danger of proximal extension of the thrombus. If bilateral sympathectomy is performed, the approach should be transperitoneal, through a median incision, in order to conserve collateral arteries coursing between and in the muscles of the flanks.

(TO BE CONCLUDED)

PLASMA FIBRINOGEN CONCENTRATION IN OCCLUSIVE ARTERIAL DISEASE

By G I C INGRAM, M D , M R C P *

(*Department of Surgery, University of Edinburgh*)

AN increased plasma fibrinogen concentration has been reported in occlusive arterial disease. In a series of 10 cases of thrombo-angitis obliterans, Friedlander and Silbert (1931) found a mean concentration of 0.56 g per 100 ml plasma (g per cent) and in 29 cases (one febrile) Sposito *et al* (1947) found a mean concentration of 0.59 g per cent, which they regarded as a moderate increase above normal.

A correlation with clinical features has not been reported.

EXPERIMENTAL

The plasma fibrinogen concentration was determined in 32 male cases of obliterative arterial disease aged 24-66 years. In each case the Wassermann reaction was negative, anticoagulants were not being given at the time of the determinations, although some patients may have been taking salicylates for the relief of pain. The fibrinogen estimations were made as fibrin, either by the micro-Kjeldahl nitrogen method (6 cases) or by the dry weight of clot method (26 cases). Previous work had suggested that these methods gave equivalent results, and the "Student"-Fisher *t*-test showed an insignificant difference between the means of the two groups above ($0.1 < P < 0.2$).

For comparison with normal fibrinogen concentrations, 30 determinations by the second method were made on plasmas from male blood transfusion donors, presumed healthy, aged 19-48 years. Further normal values were obtained from the literature.

For comparison with high pathological values, determinations were made on 4 deeply jaundiced patients and on 6 patients with gross inflammatory lesions, none showing evidence of arterial disease, selected on the likelihood of finding very high fibrinogen concentrations (Gram, 1922, Linton, 1932, Ham and Curtis, 1938). These ten determinations also were made by the second method.

RESULTS

(1) *Normal range*—The findings in the present normal series and the data obtained from the literature are shown comparatively in Table I.

In each of the four series to which the test could be applied, the correlation between fibrinogen concentration and age was positive and in two it was significant, but it was verified that the magnitude of

* In receipt of a grant from the Medical Research Council

the effect was negligible when compared to differences between the three main clinical groups studied

Two further estimates of the mean normal fibrinogen concentration

TABLE I

Plasma Fibrinogen Concentrations in Normal Males

Four published series and the present series

Source of Data	Number of Tests	Limits of Age in Years	Plasma Fibrinogen Concentration		Correlation with Age
			Mean Concentration \pm Standard Error where known g per cent	Range of Concentration (Standard Deviation Parenthesised where known) g per cent	
Gram (1922)	25	19-69	0.27 ± 0.01	$0.20-0.36$ (0.046)	Significant $r = +0.427$, $0.02 < P < 0.05$
Foster (1924)	23	3-63	0.34 ± 0.01	$0.26-0.45$ (0.049)	Not significant $r = +0.100$, $0.6 < P < 0.7$
Greisheimer <i>et al</i> (1929) (1)	213	7-94	0.33 ± 0.01	$0.20-0.80$ (0.084)	Significant $r = +0.460$, $P < 0.01$
Greisheimer <i>et al</i> (1929) (11)	106	18-50	0.29 ± 0.01	$0.20-0.55$	(Not given)
Ham and Curtis (1938)	19	25-61	0.25	$0.19-0.33$	"No outstanding" correlation
Present series	30	19-48	0.28 ± 0.01	$0.21-0.36$ (0.039)	Not significant $r = +0.233$, $0.2 < P < 0.3$

The first series from Greisheimer *et al* includes the second. Similar data are given by Lewinski (1903, quoted by Greisheimer *et al*), McLester (1922), Starlinger and Winands (1928 but mostly females), Burke and Weir (1933 but mostly from abnormals) and by Edsall *et al* (1944).

r = Correlation coefficient

P = Probability of obtaining, by chance, a result more extreme than that observed

TABLE II

High Pathological Plasma Fibrinogen Concentrations

Clinical Condition	Number of Patients	Plasma Fibrinogen Concentration (g per cent)	
		Mean \pm S.E.	Range
Deep jaundice	4	0.63 ± 0.07	$0.45-0.81$
Gross inflammation	6	0.77 ± 0.10	$0.57-1.15$

The mean concentrations of the two groups do not differ significantly

S.E. = Standard error of the mean

(Friedlander and Silbert, 1931, Sposito and Giannico, 1948) significantly higher than those shown in Table I, will be noted below.

(2) *Inflammatory conditions and jaundice without arterial disease* —

The data obtained from these patients is given in Table II. It will be seen that the plasma fibrinogen concentrations found were of the order of twice to four times the mean normal concentration.

(3) *Obliterative arterial disease*—The results obtained in the cases of the present series are compared in Table III with the data given by Friedlander and Silbert (1931) and by Sposito *et al* (1947). The age distribution of their cases is not given by Friedlander and Silbert, but is seen to be closely similar in the other two series the difference is technically insignificant.

It might appear that the fibrinogen concentrations in the cases described by the American and by the Italian workers were considerably higher than in the three cases of the present series, but it is seen from Table III that their mean normal values are also higher than the mean value obtained from the present normal series. Expressed as per-

TABLE III

Plasma Fibrinogen Concentrations in Occlusive Arterial Disease

The findings of Friedlander and Silbert (1931) and of Sposito *et al* (1947) compared with those of the present series

Series	Number of Patients	Pathological Material				Mean Normal Plasma Fibrinogen Concentration Given as (g per cent)
		Age Distribution of Patients (years)		Plasma Fibrinogen Concentration (g per cent)		
		Mean \pm S E	S D	Mean \pm S E	S D	
Friedlander and Silbert (1931)	10			0.56 \pm 0.029	0.09	0.43 (mean of single determinations in four persons)
Sposito <i>et al</i> (1947)	29	40.7 \pm 1.8	9.5	0.590 \pm 0.022	0.118	0.4 (Sposito and Gianico, 1948 derivation not given)
Present series	32	42.4 \pm 1.6	9.3	0.368 \pm 0.017	0.099	0.28 \pm 0.01 (Table I)

S E = Standard error of the mean

S D = Standard deviation

centages of their respective normal values, the mean pathological values of the three series become —Friedlander and Silbert, 130 per cent, Sposito *et al*, 147 per cent, present series, 131 per cent. The difference between the raw mean values of the two reported series is technically insignificant, it is perhaps hardly justifiable to make a more precise comparison between these values and the corresponding mean value of the present series, than that given above in relation to their respective mean normal values, the three groups of pathological data appear comparable.

Correlation with clinical characteristics

The fibrinogen concentrations found in the present series were studied in relation to various clinical features.

(1) *Incidence of migratory phlebitis* (Table IV)—Five patients showed active migratory phlebitis at the time of the determination, 4 others were known to have had the condition in the past but were

quiescent in this respect when tested, the remaining 23 were without known migratory phlebitis at any time. Taking the mean ages of the groups, the 5 patients with active phlebitis were significantly younger than the 23 patients never known to have had the condition, the 4 with quiescent phlebitis were of intermediate age. Despite this clear distinction between the first and the third groups (corresponding to a clinical differentiation of thrombo-angitis obliterans from arterio-sclerotic arterial occlusion), the mean plasma fibrinogen concentrations of these two groups did not differ significantly.

(2) *Duration of arterial occlusion when tested*—At the time of the determination, there was evidence in all cases of established arterial insufficiency, although in 2 the clinical picture also suggested that a

TABLE IV

Plasma Fibrinogen Concentrations in Occlusive Arterial Disease
Classification by incidence of migratory phlebitis

Incidence of Migratory Phlebitis	Number of Patients	Age (years)		Plasma Fibrinogen Concentration (g per cent)	
		Mean \pm S F	S D	Mean \pm S E	S D
Active when tested	5	36.2 \pm 2.8	6.3	0.330 \pm 0.031	0.069
Previously active but quiescent when tested	4	40.5 \pm 2.0	4.0	0.388 \pm 0.021	0.041
Without known phlebitis	23	42.7 \pm 2.1	10.1	0.373 \pm 0.023	0.111

The difference between the mean ages of the first and third groups is significant ($0.01 < P < 0.02$)

S E = Standard error of the mean

S D = Standard deviation

P = Probability of obtaining, by chance, a result more extreme than that observed

further spread of the arterial lesion had recently occurred. One man, aged 44 years, who had suffered from intermittent claudication in the left leg but without impairment of the nutrition of the skin, suddenly developed pain in the same leg and noticed pallor in the foot. Tested eleven days after this event, his plasma fibrinogen concentration was found to be 0.62 g per cent. The leg required amputation three weeks later. The other man, a Pole aged 24 years, developed ulceration of the great toe of the affected leg, ten to twelve days after the onset his plasma fibrinogen concentration was found to be 0.47 g per cent.

(3) *Incidence of gangrene*—Gangrene was known to have been present at the time of the determination in 3 patients in whom the plasma fibrinogen concentrations were found to be 0.22, 0.47 and 0.71 g per cent. The second case is that mentioned above, in the third case the lesion was infected. This concentration was the highest recorded in the series.

(4) *Incidence of other inflammatory lesions*—In addition to the

patient with infected gangrene, minor inflammatory lesions were found in 3 patients at the time that the determination was made the plasma fibrinogen concentrations were 0.37, 0.39 and 0.43 g per cent

(5) *Incidence of epidermophytosis pedis*—Fungus infection of the feet has been thought important in the natural history of arterial occlusion. At the time of the determination, clinical evidence of epidermophytosis pedis was present in 4 patients. The plasma fibrinogen concentrations were 0.22, 0.34, 0.34 and 0.62 g per cent, the fourth case being that described in Section (2) above.

Thus, the two highest fibrinogen values in the series, 0.71 and 0.62 g. per cent, occurred respectively in a case with infected gangrene and in a case with gross impairment of tissue nutrition, also, a patient with a gangrenous ulcer gave a value of 0.47 g per cent. With one exception (0.48 g per cent in a man of 62 years) no other case in the series presented a fibrinogen concentration above 0.44 g per cent.

DISCUSSION

(1) *Normal range of fibrinogen concentration*—It appears that the mean normal plasma fibrinogen concentration rises slightly with age, but it has not been found necessary in the present work to consider age differences when comparing the fibrinogen concentrations of the three main clinical groups.

The normal fibrinogen concentrations given by Friedlander and Silbert (1931) and by Sposito and Giannico (1948) are considerably above the other values studied in Table I. The difference may be observational rather than physiological but in any case somewhat obscures the interpretation of pathological data. Elsewhere, the latter authors (Sposito and Giannico, 1944) ascribe their fibrinogen determination to M. Lassier, who obtained the dry weight of fibrin formed by the spontaneous clotting of native plasma centrifuged in the cold (described by Lian and Frumusan, 1938, who gave the normal range by this method as slightly above 0.4–0.5 g per cent).

(2) *Fibrinogen concentration in occlusive arterial disease*—From a comparison with the normal and with the grossly pathological ranges of the present series, it is clear that the range of fibrinogen concentration found in the cases of arterial occlusion is moderately increased above normal (confirming the finding of Sposito *et al*, 1947, in relation to their own normal value).

The relation of plasma fibrinogen concentration to clinical features

Analysis of the cases of the present series according to the incidence of phlebitis, gangrene, minor inflammatory lesions or of epidermophytosis pedis fails to demonstrate a simple relationship between the plasma fibrinogen concentration and any of these features. It is seen that three of the four highest fibrinogen concentrations recorded were

associated with overt inflammatory states. Although 2 of these patients are thought to have suffered a recent exacerbation of their arterial lesions, it seems likely that their high fibrinogen concentrations were an indirect result rather than the cause of the process.

By an extension of this argument, the other evidence presented suggests that the less markedly raised fibrinogen concentrations found in the majority of cases in this series represent milder inflammatory reactions to the disease process. This is in line with the well-known response of the plasma fibrinogen concentration to inflammatory states in general (Gram, 1922, Foster, 1924, etc). It is thus not necessary to postulate that a high plasma fibrinogen concentration predisposes to thrombosis. This accords with the findings of Meyers (1948) in 28 cases of coronary infarction and with the recently-expressed view of Quick (1951).

SUMMARY

Plasma fibrinogen concentrations have been determined in 32 cases of occlusive arterial disease, including 9 cases with, or having had, migratory phlebitis. Comparison with concentrations in normal individuals and in patients with gross inflammatory lesions and with jaundice showed the concentrations found in the arterial occlusion group to represent a moderate increase over normal. The increase was not found to be specifically related to thrombotic manifestations but was thought to represent a non-specific inflammatory reaction.

It is a pleasure to acknowledge my indebtedness to Dr C. C. Burt for the provision of clinical data, to Dr R. A. Cumming, Regional Director of the South East Scotland Regional Blood Transfusion Service, for the provision of normal blood samples and to Dr P. Armitage of the Medical Research Council Statistical Research Unit, London School of Hygiene, in the analysis of the numerical data.

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A STUDY OF 200 CASES OF APPENDICITIS WITH SPECIAL REFERENCE TO THEIR BACTERIOLOGY

By A F MACCABE, M D , D P H

(*Department of Bacteriology, University of Edinburgh*)

and

JOHN ORR, F R C S E

(*Peel Hospital, Galashells*)

DURING a period of thirty-three months—from July 1948 to March 1951, 1172 appendicectomies were performed at Peel Hospital. At one period in late 1949 and early 1950 there was a considerable increase in the average number of cases of acute appendicitis, many of which were gangrenous, so that we wondered whether there could be any specific micro-organism acting as the causal agent in what appeared to be a minor epidemic. In view of this, a bacteriological investigation was carried out on 200 appendices, the majority of which were acutely inflamed.

CLINICAL

Table I gives the age and sex incidence of the 200 cases examined.

TABLE I

	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	Over 80	Total
Males	4	30	24	15	11	7	1	2		94
Females	4	35	28	15	10	10	2	1	1	106
Total	8	65	52	30	21	17	3	3	1	200

Many writers in the past have investigated the sex-ratio and have come to the conclusion that appendicitis is more frequent among males than females. Moloney *et al* (1950) found that there were 591 males and 483 females admitted with true appendicitis to the Radcliffe Infirmary, Oxford, during the four years 1945-48. Our figures, limited to the 200 cases under bacteriological review show a reversal of the usual findings in this respect. Table I shows that appendicitis is essentially a disease of people under 50 years, the average age being 28 years. In 41 per cent of cases it was the first attack of abdominal pain from which the patient had suffered. Of the 24 patients over 50 in only 7 was this the first attack of pain with which they were admitted. In 73.5 per cent there had been nausea and/or vomiting. On arrival in hospital the temperature was elevated in 19 per cent of cases and the pulse rate was increased in 19.5 per cent of cases. These last two findings illustrate how temperature and pulse rate are not often helpful in the early diagnosis of acute appendicitis. In the majority of cases the

history and clinical examination findings as far as routine textbook descriptions are concerned were atypical. These "atypical" histories and findings may well be in part the result of the position in which the appendix was found at operation.

During the period of thirty-three months there were 6 deaths following appendectomy from the following causes. General peri-

TABLE II

Organisms Present in	No Organisms Found	Pu Present in	Gangrenous	No Pus or Exudate	Normal
97 per cent	3 per cent	57 per cent	20.5 per cent	8.5 per cent	14 per cent

TABLE III

Frequency of Particular Bacterial Groups or Species from Diseased Appendices

Organisms	Times Isolated (per cent)	Alone (per cent)	Predominant (per cent)	Isolated Wall (per cent)	From Contents (per cent)
Coliform bacilli	96	21	82	65	68
<i>Strept. faecalis</i>	46	0.5	3	36	38
<i>Lactobacillus acidophilus</i>	27			23	24
<i>Alkaligenes faecalis</i>	1			1	1
<i>Clostridium perfringens</i>	11			4	9
Other clostridia	8			4	8
<i>Bacteroides</i>	10		0.5	8	9
<i>Strept. anaerobius</i>	4			2	2
<i>Proteus vulgaris</i>	2			1	1
<i>Pseudomonas aeruginosa</i>	2		1	1	1
<i>Micrococcus pyogenes albus</i> (c-)	14			11	10
<i>Micrococcus pyogenes albus</i> (c+)	1			1	
<i>Micrococcus pyogenes aureus</i> (c-)	1			1	1
<i>Micrococcus pyogenes aureus</i> (c+)	2		1	2	2
<i>Strept. mitis</i>	2			2	2
<i>Diplococcus pneumoniae</i> Type 1	0.5			0.5	0.5
<i>Diplococcus pneumoniae</i> Type 19	0.5				0.5
<i>Diplococcus pneumoniae</i> Type 23	0.5	0.5	0.5	0.5	0.5
<i>Haemophilus influenzae</i>	0.5			0.5	0.5
Diphtheroids	3			3	2

c = coagulase

tonitis (2) aged 14 and 24, paralytic ileus (2) aged 45 and 50, multiple liver abscesses (1) aged 41, general debility (1) aged 68 (died five days after operation). It should be noted from the ages of these 6 patients that none of them had attained their three score years and ten.

BACTERIOLOGICAL EXAMINATION

The appendix was removed from its container with sterile forceps and placed in a sterile tray. Using sterile instruments the appendix was opened in its entire length to expose the mucous membrane

Specimens were taken (1) from the contents (fæces, pus, etc.) if present, and (2) the inner wall of the appendix (after pus, fæces, etc., had been thoroughly removed) by scarifying the mucous membrane and penetrating into the submucosa with a sharp instrument. The following media were inoculated—blood agar, glucose blood agar, MacConkey's, and cooked meat medium (bullock's heart). Both aerobic and anaerobic methods of cultivation were employed. Film preparations were also made from the contents and wall, and stained by Gram's method in order to study the exudate.

After incubation at 37° C for twenty-four, forty-eight, and in some cases seventy-two hours, the inoculated media were examined. The results are shown in Tables II, III and IV.

TABLE IV
Species Isolated from the 28 Normal Appendices
(22 Contained Organisms)

	Times Isolated	Alone	Predominant	Wall	Contents
Coliform bacilli	22	5	15	12	12
<i>Strept. faecalis</i>	9			7	7
<i>Lactobacillus acidophilus</i>	5			5	4
<i>Clostridium perfringens</i>	2			1	2
Other clostridia	3			2	1
<i>Streptococcus anærobius</i>	1			1	1
<i>Micrococcus pyogenes albus</i> (c—)	4	1	1	3	3
<i>Strept. mitis</i>	2			1	1

DISCUSSION

The most important causative factors in the ætiology of acute appendicitis are obstruction of the appendicular lumen and infection (Boyd).

While it is possible for obstruction *per se* to cause appendicular disease, the presence of bacteria in an otherwise normal appendix may not by itself give rise to appendicitis. Wilkie (1931) emphasised the importance of obstruction and not inflammation in fatal cases of appendicular diseases, and he stressed the danger of a sudden and complete obstruction of the appendix containing fæcal matter which could lead to tension gangrene from pressure, followed by perforation. In this type of case, by no means rare, it would not seem likely that any bacteria present would have time to play a major part in the morbid process. Wagenstein and Dennis (1939) maintained that the obstructed and exteriorised human appendix could develop a secretory pressure almost equal to systolic blood pressure.

It was shown by Wells (1947) in experimental work in rabbits, that intravenous injection or the introduction into the appendix of such organisms as non-hæmolytic streptococci, anaerobic bacilli from human inflamed appendices, emulsion of purulent contents of human appendices, or hæmolytic streptococci from the throats of cases of

tonsillitis, all failed to produce acute appendicitis. Wells stressed the importance of preliminary damage to the mucous membrane as being a factor in the production of acute appendicitis. Obstruction of the lumen with a damaged mucous membrane was always followed by acute inflammation and death of the animal—the damage to the mucous membrane may be quite trivial. Nigam (1947) also demonstrated in experimental work how intravenous or intraluminal injections of virulent streptococci sometimes failed to cause any gross or even microscopical lesion in the appendix.

What role then do bacteria play in the ætiology of acute appendicitis? Many different species of bacteria can be found both in the healthy and diseased appendix. This is well illustrated in the results of the present investigation. The important points for discussion in this respect are (1) the origin of these micro-organisms, and (2) the pathogenicity of the various species. Three main views have been put forward regarding the origin of infection in appendicitis, (1) enterogenous (Weinberg *et al*, 1928), (2) intrinsic (Aschoff, 1931), while (3) Poynton and Paine (1911), Rosenoff (1916) and Wakeley and Childs (1950) favour the hæmatogenous route. Rosenow stresses the possibility of a focus of infection of streptococci in the teeth or tonsil, the organisms developing a selective affinity for the appendix. It was, however, pointed out by Aschoff in 1931 that the principal organisms present in the tonsil and appendix both in health and disease are different—hæmolytic streptococci being found in the tonsil and non-hæmolytic streptococci (*Strept. faecalis*) in the appendix. Again, it is observed that most attacks of acute appendicitis are unconnected with any preceding illness, nor is there a rise in cases of appendicitis in conditions of septicæmia or during such epidemics as acute tonsillitis. In the present series only one case had a history of recent tonsillitis. Moreover, Bowen (1943) did not find any suggestion of an epidemic character in his statistical survey of appendicitis.

This investigation has shown the large variety of bacterial species that can be found in the appendix. It also illustrates that the majority of species found in both the diseased and healthy appendix are those which are found as commensals in the healthy intestinal tract. It would appear that the following organisms might be able to cause appendicitis, viz. coliform bacilli, *Strept. faecalis*, bacteroides group, pneumococcus, *Ps. aeruginosa* and *M. pyogenes aureus*—these organisms being found alone or as the predominant species in diseased appendices. However, primary place must be given to the coliform bacilli for the following reasons—(1) they were found alone in 21 per cent cases, (2) predominant organisms in 82 per cent cases, (3) found alone in 11 per cent purulent cases, (4) only 3 of the 113 appendices containing pus did not contain coliform bacilli, (5) coliform bacilli were present in all gangrenous cases and found alone in 3 per cent of such cases, (6) in 4 cases of appendix abscesses coliform bacilli were present in all 4 and were predominant in 2.

The next most frequent species isolated was *Strept faecalis*. This organism was isolated alone in 0.5 per cent cases and was the predominant species in 3 per cent. It is possible that it may play an important role in initiating a pathological condition in the appendix, but only in a very small percentage of cases. Aschoff (1931) stressed the importance of *Strept faecalis* as being a causal agent in appendicitis and he maintained there were increased numbers of this organism in the distal part of the organ. We, however, believe that coliform bacilli are more important in initiating the morbid process—a view also held by Weinberg *et al* (1928) who showed how a few *Esch coli* could greatly increase the virulence of *Strept faecalis*. Our findings are similar to those of Weinberg *et al* in that the most frequent combination was *E coli* and *Strept faecalis* alone, or in association with other organisms. *Proteus* and *Ps aeruginosa* can be found in the intestine and occasionally may give rise to pathological conditions. In this investigation they did not play a dominant role in the infection.

As regards the anærobic bacteria it does not appear that any of these by themselves can cause appendicitis, only one species—a *Spherophorus necrophorus*-like organism Bacteroides group—being found predominant and in only 0.5 per cent cases, and none being found alone. There is no doubt they play a great part in furthering the pathological process, once begun. All the anærobic species isolated in this investigation can be found in the normal bowel. Some, such as *Spherophorus necrophorus* and *Bacteroides fragilis* are definitely associated with gangrenous and suppurative conditions in certain parts of the body, but it is not known whether they are the primary ætiological agents. In the conditions of appendicitis it appears they are not the primary agents, but require the presence of other species to initiate the process or perhaps to increase their virulence. Matt (1950) obtained a pure growth of *Spherophorus necrophorus* from an intra-abdominal abscess in a case of acute segmental ileitis. Dack *et al* (1937) found *Spherophorus necrophorus* the predominant anærobic organism in 3 out of 4 cases of chronic ulcerative colitis. Anærobes in the present investigation were found in 30 per cent gangrenous and in 20 per cent non-gangrenous cases. The commonest anærobe isolated was *Cl perfringens*. This was also the experience of Weinberg *et al*, and they showed how *Esch coli* could increase the virulence of *Cl perfringens*.

It appears that the normal intestinal commensals take on a pathogenic role under certain circumstances. How they do this is not clear. It may be that such factors as stagnation of contents, or appendicular secretion, or the presence of other bacterial species may increase their virulence, *i.e.* a symbiotic virulence enhancement. We believe that coliform bacilli are the primary cause of the inflammation in the majority of cases. Such conditions as obstruction with its accompanying increased intra-luminal pressure and stagnation of contents would cause devitalisation of the mucous membrane leading to loss of equi-

librium between virulence of the organism and resistance on the part of the mucous membrane, resulting in a state of affairs favourable to the organism. According to Dennis (1941) inflamed appendices present an average resistance to outflow three times normal. One must not regard virulence as some specific intrinsic quality of the particular species, but rather the summation of factors both on the part of the organism and host which results in a condition more favourable to the bacteria.

Bohning (1931) suggests that any disturbance in the self-cleansing of the secretions of the appendix will lead to increase in virulence, and she maintains that the bacterial flora of the appendix during digestion and starvation are different, and it also changes in various diseases which hinders the development of appendicitis.

Staphylococci can be found in normal fæces. On routine media, however, they tend to be overgrown by *Esch. coli*. This can be overcome by using a selective medium.

It is not usual to find pneumococci in the normal intestine, as the presence of bile would be inhibitory. In one case, however, *Pneumococcus* type 23 was isolated alone both from the wall of the appendix and the contents, and one can only assume that this organism played a major part in the inflammatory reaction which was of the chronic type. The question arises by what route the pneumococcus reaches the appendix from its initial locus in the upper respiratory passages. This organism is not likely to reach the appendix via the stomach and small intestine—a hæmatogenous origin of the infection seems more likely.

The isolation of a hæmophilic organism (*Hæm. influenzae*), although not the predominant organism in the particular case, was interesting, in that we can find no previous record of a hæmophilic species having been isolated from the appendix. This type of organism normally inhabits the upper respiratory tract. The same question arises in this case as in the case of the pneumococcus.

The infection in appendicitis, therefore, appears to be endogenous in origin. We believe that anatomical and/or physiological damage to the mucous membrane is an important factor, and in conjunction with stagnation of contents and appendicular secretion will be favourable to the bacteria present. It is easy to imagine how the mucous membrane is subject to repeated trauma on account of the mobility of the appendix particularly when associated with bands or adhesions, and also on account of the easy access of intestinal contents which must return to the bowel via the same route. We believe that the intestinal organisms gain access to the wall of the appendix from the lumen, through either an anatomical breach or a physiologically devitalised part of the mucosa, and that these changes in the mucosa are primarily brought about by the obstructing agent—fæcolith, foreign body, adhesions, threadworms, spasm, kink, etc., and pressure distension distal to the obstruction. This weakened mucous membrane allows any organisms

present to establish themselves and by taking advantage of this abnormal state produce their effects. Appendicitis affords an example of a condition caused by organisms which in one part of the body are pathogenic, yet in another are quite harmless.

Neither *Ent histolytica* nor *Actinomyces* was isolated from any specimen. The absence of these organisms is in part responsible for the fact that there was no case in this series in which fæcal fistula developed post-operatively. In contrast to Raftery, Trafas and McClure (1950) who found *Histoplasma capsulatum* in 5 per cent of 2, 135 appendices, this organism was not found in any of our cases.

The findings in this investigation do not show that this special prevalence of appendicitis was due to any particular species of micro-organism. Whether there was some as yet unknown specific factor responsible for damaging the mucous membrane of the appendix other than an obstructing agent is not known.

Aschoff believes that most people suffer from one or more attacks of acute appendicitis during life, and although the appendix may not appear abnormal by macroscopic and routine microscopic examination, nevertheless, by the employment of special methods it often shows signs of inflammation.

In 1889 Charles McBurney wrote —“What we wish to accomplish in the treatment of appendicitis is not to save half of our cases, not four cases out of five, but all of them.” After sixty-two years of very considerable progress, this aim has not yet been accomplished, and it is our opinion, that early surgery combined if necessary with chemotherapy is the only way to attain this objective, as we are unable to deal with the appendicular obstruction other than by operation and the organisms responsible are already in the lumen waiting their chance to cause appendicitis. We agree with Boyce (1951), Schullinger (1950) and many others that there is no place for the treatment of acute appendicitis with chemotherapy without operation, as this will not stop the disease from progressing, and will often mask the development of complications. Perhaps Moloney, Russell and Wilson (1950) are theoretically correct when they asked whether “the safety of appendicectomy had not in some measure hampered the growth of clinical judgment,” but as long as there are many deaths annually (152 in Scotland in 1950 and 1252 in England and Wales in 1949) and so long as appendicitis tends to present itself in “atypical” forms and often mimic other abdominal diseases, and so long as early appendicectomy is associated with virtually no mortality, we consider this to be the only justifiable treatment where there are reasonable grounds for the diagnosis of acute appendicitis.

SUMMARY

1. Some of the important clinical and operative features are given in 200 cases of appendicitis, the appendices of which were examined bacteriologically.

2 Bacteriological examination revealed that the commensals of the bowel were present in the wall of the appendix in cases of appendicitis Coliform bacilli were the predominant organisms

3 From 28 normal appendices intestinal commensal bacteria were isolated in 22 cases The flora from the wall and contents showed no appreciable difference

4 It is our opinion that the bacteria gained access to the wall of the appendix through a breach in a devitalised portion of the appendicular mucosa

5 Early surgery combined, if required, with chemotherapy is the treatment of choice in acute appendicitis

We express our thanks to Mr Quarry Wood for his advice and interest in this investigation, and to Dr Levinthal for his typing of the pneumococci

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NOTES

AT a Graduation Ceremonial held in the Upper Library on Friday,
 14th December 1951, the following degrees were
 conferred —
University of Edinburgh

The Degree of Doctor of Medicine —Percy Francis de Caires, British Guiana, M P M , M B , CH B , 1938 (*In absentia*), Robert McKenzie Fulton, Scotland, M B , CH B (with Honours), 1942 (*Highly Commended for Thesis*), Christopher Eberhard Ludwig Haffner, England, M B , CH B , 1944 (*In absentia*), Thomas Harrison, England, M B , CH B , 1921 (*In absentia*), Harry Oswald-Smith, Scotland, M B , CH B , 1900, Alistair Sutherland Livingston Rae, Scotland, M B , CH B , 1935, Alan Robert Somner, Scotland, M B , CH B , 1946 (*Highly Commended for Thesis*)

The Degree of Doctor of Philosophy—*In the Faculty of Medicine* — Deb Prasanna Basu, M B , B S (CALCUTTA), Aubrey Stanislaus Outschoorn, M B , L M S (CEYLON)

The Degrees of Bachelor of Medicine and Bachelor of Surgery —Audrey Nora Henderson Andrew (*nee* Robertson), Scotland, William Robert Cameron Andrew, Scotland, Eric Sutton Blackadder, Scotland, Frank Keppie Paterson Brydon, Scotland, Robert Christie Buchanan, Scotland, Isobel Catherine Campbell, Scotland, George Malcolm Dewar, Scotland, Johannes Marthinus Petrus Dippenaar, South Africa, William Fyfe Morrison Dorward, M A , Scotland, Margaret Joyce Field, B S C , PH D England (*In absentia*), Peter Traill Fraser, Scotland, Paul William Eardley Hayward, England, Roman Stanislaw Jarema, Poland, John Harold Jennings, England, Donald Ferguson Kerr, Scotland, Margaret Livingstone Liddell, Scotland, Douglas Watson Lyon, Scotland, Mary Iona McArthur, Scotland, Ranald Macdonald, England, Malcolm Alexander McFadyen, Scotland, Dennis Wenceslas Maxa, Scotland, Alexander Edwin Meek, Scotland, Charles Cameron Moir, Scotland, George Dimond Earngey Morris, Scotland, Johan Ekhard Munro, South Africa, Alexander Euan Mackay Reekie, Scotland, William Douglas Riddell, Scotland, Adam Alan Robertson, Scotland, Albert Henry Ian Scott, Scotland, William Allan Simpson, Scotland, Robert More Stewart, Scotland, John Hugh Sutherland, Scotland, George Peter Syme-Thomson, England, John Millar Tansh, Scotland, Jean Caverhill Taylor, Scotland, Charles Graeme Marshall Thrd, Scotland, Frederick Augustus Viapree, Scotland, Frederic Eustace Berkeley Wills, British Guiana

Diploma in Medical Radiodiagnosis —Alan Lien-yiu Chen, M B (WEST CHINA UNION), James MacGregor McKay, M B , CH B (ABERD), Mihir Kumar Mitter, M B (CALCUTTA)

Diploma in Medical Radiotherapy —Walter Disney Rider, M B , CH B

Sister-Tutor Certificate —Ellen Mona Haigh, Margaret Mary Hannon, Bertha May Hawkins, Ena Isobel Leiper, Anne McSharry, Sarah Matthew, John Kendrick Minks, Winifred Catherine MacIldowie Potter

The Vans Dunlop Scholarship in Forensic Medicine and Obstetrics — John Patrick Laidlaw

The Llewellyn Bevan Prize —James Farquhar Ogilvie Mitchell, M D

The Goldie Prizes for Dental Mechanics —First Prize—Ronald James Gutteridge, Second Prize—Eric Arthur Binnie Gibson

The Tindal Scholarship —Robert Burrows, B SC, M R C V S

At a meeting of the Royal College of Surgeons of Edinburgh held on

Royal College of Surgeons of Edinburgh 19th December 1951, Professor Walter Mercer, President in the Chair, the following who passed the requisite examinations were admitted Fellows —Thomas Laird

Barclay, M B, CH B, UNIV EDIN 1947, Francis Bauer, M D, UNIV PRAGUE 1938, L R C S EDIN 1948, Lydia Colaco, M B, B S, UNIV MADRAS 1942, Joseph Kevin Craig, M B, CH B, UNIV MANCH 1946, Hugh Arnold Freeman Dudley, M B, CH B, UNIV EDIN 1947, Alan Stoddart Lambert, M B, CH B, UNIV NEW ZEAL 1946, Daniel Gerard Lane, M B, B S, UNIV QUEENSLAND, AUSTRALIA 1947, Francis Douglas Martinson, M B, CH B, UNIV EDIN 1942, Shreemohan Mishra, M B, B S, UNIV PATNA 1947, Archibald Hope McCallum, M B, CH B, UNIV CAPE TOWN 1945, John Andrew McCredie, M B, B CH, B A O, QUEEN'S UNIV BELFAST 1946, Ian Grant Mackenzie, M B, CH B, UNIV EDIN 1946, M D 1948, Satya Nand, M B, B S, UNIV PUNJAB 1948, William Harford Rutherford, M B, B CH, TRINITY COLL DUBLIN 1944, Leo Stein, M B, CH B, UNIV WITWATERS-RAND 1943, Daniel Pieter Viljoen, M R C S ENG, L R C P LOND 1932, James Alfred Scott Wilson, M D, C M, DALHOUSIE UNIV CANADA 1948

Fellows in Dental Surgery —Professor Robert Humphrey McKeag, M A, M B, B CH, B A O, B DENT SC, Department of Dental Surgery, University of Ceylon was elected a Fellow in Dental Surgery without examination, and John Stevenson Howie, B D S, UNIV NEW ZEAL was elected a Fellow after examination

NEW BOOKS

Electron Microscopic Histology of the Heart By BRUNO KISCH, M D Pp vi+106 illustrated New York Brooklyn Medical Press 1951 Price \$5 00

The author, using sections between 0.1 and 0.2 μ in thickness, has studied the finer structure of the heart. His findings are beautifully shown by microphotographs of the tissues. This difficult and detailed work may open up a fuller understanding of the muscle of the heart and of the action of drugs on it.

A Text-Book of Medicine Edited by E. NOBLE CHAMBERLAIN, M D, M SC, F R C P Pp xii+962 Bristol John Wright & Sons 1951 Price 50s

It is most fitting that Noble Chamberlain has now produced a text-book of medicine forming a companion volume to his well known *Symptoms and Signs*. Those who know his previous work will enjoy in his latest book the clarity of description which, if at times dogmatic, allows easy reading and understanding for the undergraduate. Each disease is described under ætiology, pathology, clinical findings, diagnosis and treatment. The last in many cases is brief and, with such rapid progress in therapeutics, it is felt that an additional chapter on the antibiotics would have been of great service, especially to the general practitioner.

It is generally held that American publications are all round better productions than the British counterpart in regard to text and illustrations. It is refreshing and heartening to see that in this book such an opinion is completely refuted.

Venereal Diseases Described for Nurses By R C L BATCHELOR, M A, M B, CH B, F R C S E D, M R C P E, D P H, and MARJORIE MURRELL, M B, B S, M R C S, F R C S E D, D P H Pp 111+217, with 43 figures Edinburgh E & S Livingstone 1951 Price 12s 6d net

This excellent small volume, although intended for the nursing profession, does itself an injustice by using the latter qualification in its title page. Its concise and well-illustrated text describes the onset, progress, commonly associated diseases and the more conservative methods of treatment. Over all it produces a masterly and composite picture which the student, practitioner or postgraduate, with limited reading time, will not find in any other textbook of Venereology.

The Electrical Activity of the Nervous System By MARY A B BRAZIER, B SC PH D Pp 220, with 96 illustrations London Pitman 1951 Price 25s net

Although this book is entitled a Textbook for Students, it contains far more than a medical student can be expected to cover. It is neither accurate nor critical enough for students in a Final Honours Course in Physiology, but students for higher degrees which require a knowledge of neurophysiology may find the chapters on the ear and the eye useful. The chapters on the cortex and electroencephalogram contain a useful guide to the recent literature which is as yet incompletely dealt with in standard textbooks.

The Mode of Action of Anæsthetics By T A B HARRIS, M B, B S, D A, F F A Pp 111+768, with 22 figures Edinburgh Livingstone 1951 Price 42s net

The reviewer considers that in many respects this book on anæsthesia may be regarded as one of the best ever published. In it the author has crystallised the fruits of years of painstaking research of the literature of basic and clinical medical science. The chemistry and pharmacology of the many agents employed in anæsthesia are explained in detail rarely seen except in special journals. A working hypothesis of the mode of action of anæsthetics is presented and forms a reasonably credible basis for the clinical section of the book. Although the style is frequently repetitive this appears to be purposely designed as a mode of emphasis. This volume will be of the highest value to students and teachers and will help both to a better understanding and appreciation of the complex scientific aspects of a subject which until recent years many have been content to regard as merely an art.

Law relating to Hospitals and Kindred Institutions Supplement to 1949 (Second Edition) By S R SPELLER, LL B Pp viii+87 London H K Lewis 1951 Price 12s 6d net

This publication has no separate existence as a book but is merely to bring the second edition up to date. It is supplementary to the parent volume. A number of new subjects have been introduced, including the licensing of official motor cars, cinematographs in hospitals and area Nurse-training committees. The subject-matter deals only with English Law.

Bronchial Asthma—Its Relation to Upper Respiratory Tract Infection By R J WHITEMAN, M B, CH B, F R A C S Pp 11+184 London H K Lewis 1951 Price 15s net

The work described in this book is entirely clinical. It is the experience of the author dealing with many cases of chronic nasal infection. The purpose of this volume is threefold: firstly an attempt to bring evidence to show that chronic nasal catarrh is the result of inadequately treated acute coryza, secondly it outlines both hospital and home treatment for nasal catarrh, especially in children, thirdly it shows the application of this treatment to patients suffering from hay fever and asthma.

Asthma is a highly controversial subject. The author avoids entering into any controversy but merely shows the improvement in asthmatics when their upper respiratory tract infection is adequately treated.

Diseases of the Endocrine Glands By LOUIS J SOFFER Pp 1142, with 88 illustrations London Henry Kimpton 1951 Price 105s

This large new textbook of clinical endocrinology is from the Mount Sinai Hospital, New York. It follows the traditional style, is well written and carefully documented. Illustrative case records add to its interest. It is a pity that the appendix of laboratory tests does not contain an assessment of the value of these tests. The authority of the book may encourage an unwarranted faith in some of the methods, such as those for urinary corticosteroids. The photographs, especially those in colour, are not up to the standard of the text. It would be better to omit the term "Simmonds' Cachexia" which emphasises an inconstant feature of the disease. But these are minor criticisms, and the author is to be congratulated on his courage and skill in producing a book which should be of real value to students of endocrinology.

Major Symptoms in Clinical Medicine By JOHN ALMEYDA, M R C P, M R C S, D P H Pp viii+335 Vol II London Henry Kimpton 1951 Price 25s net

Like the first volume of this book, volume two discusses the applied anatomy and physiology of each system before the main symptoms in each section are described. This second volume contains sections on neurological, psychological, locomotor and endocrine symptoms. The whole book is written in a clear, lucid and direct style and should prove very useful for undergraduates and postgraduates.

The Thyroid By THOMAS HODGE MCGAWACK Pp 646, with 72 figures and 22 tables London Henry Kimpton 1951 Price 95s

The literature dealing with the thyroid grows rapidly. This book aims to present a large scale, up to date review of the chemistry and physiology and to analyse thyroid disease in the light of our newer knowledge. It succeeds in these aims and at the same time entertains the reader with an interesting historical section. It is a little surprising to read that patients who receive antithyroid drugs for hyperthyroidism should have a determination of the basal metabolic rate and a complete blood count before each visit to the clinic. However, there is little to criticise in the book, which is a comely and intelligent guide through the maze of papers on the thyroid.

NEW EDITIONS

Handbook of Tuberculosis Schemes in Great Britain and the Commonwealth Thirteenth Edition Pp 370 London National Association for the Prevention of Tuberculosis 1951 Price 30s net

The coming into force of the National Health Service Act has necessitated the re-writing of this Book. Tuberculous patients move about like other people, and the Tuberculosis Physician has for many years depended upon this book for information regarding the services available in other areas. He will find all that he wants to know in this new and enlarged edition.

American Illustrated Medical Dictionary By W A N DORLAND, AM, M D, F A C S Twenty second Edition Pp xxvi+1736, with many illustrations London W B Saunders 1951 Price 50s

This book which first appeared in 1900 has long been esteemed a classic. It is run by an editorial board helped by the contributions of a large number of specialists. The present edition includes thousands of new terms and scores of new illustrations which bring it up to date in the various fields of medicine and allied sciences. A valuable feature of the work is the large number of useful tables.

This standard work is probably the leading medical dictionary in the English language.

Fractures, Dislocations and Sprains By J A KEY and H E CONWELL Fifth Edition Pp 1232, with 1195 illustrations London Henry Kimpton 1951, Price 115s net

The new edition of this well-known American text-book has just appeared and though many of the least valuable illustrations have been deleted, little reduction in the book has been achieved since much new material in the way of new methods or modifications of old has been added. The authors rightly make little claim to originality, and the methods described are mostly those in general use. None the less, the book is well written and interesting to read since these methods are fully described and lavishly illustrated.

There is an admirable chapter on injuries of the spine in which all types of such injuries are fully described in an up-to-date fashion.

In other parts of the book there is much upon which surgeons in this country might have different ideas. Skeletal traction to the lower end of the femur is virtually given up here but there are many illustrations of it in the text-book. It is interesting to read of general treatment to peri-arthritis of the shoulder in the shape of "a low caloric diet, low in fats and rich in green vegetables and fruit, and a teaspoonful of sodium phosphate in a glass of water on arising in the morning". The authors believe that shoulder function in a ruptured supra-spinatus is restored without operation. It seems strange, too, to amputate in a case of congenital tibial lower third fracture.

The production of this volume is far below the standard of Scottish publishers, but it is a useful book for those for whom it is written—students, practitioners and surgeons.

BOOKS RECEIVED

- COOPE, Dr ROBERT *The Quiet Art* (*E & S Livingstone Ltd, Edinburgh*) 12s 6d net
- DAVIDSON, MAURICE, M A, D M, B CH (OXON), F R C P (LOND), and SMITHERS, DAVID W, M D (CANTAB), M R C P (LOND), D M R, and TUBBS, OSWALD S, M A, M B, B CHIR (CANTAB), F R C S (ENG) *The Diagnosis and Treatment of Intrathoracic New Growths* (*Oxford University Press, London*) 42s net
- DYKE, S C, D M (OXON), F R C P (LOND), General Editor *Recent Advances in Clinical Pathology* Second Edition (*J & A Churchill Ltd, London*) 40s net
- ELLER, JOSEPH JORDAN, B S, M D, and ELLER, WILLIAM DOUGLAS, M D *Tumors of the Skin* Second Edition (*Henry Kimpton, London*) 105s net
- HAULTAIN, W F T, OBE, M C, B A, M B, B CH, F R C P E D, F R C S E D, F R C O G, and KENNEDY, CLIFFORD, M B, CH B, F R C S E D, F R C O G *A Practical Handbook of Midwifery and Gynaecology* Fourth Edition (*E & S Livingstone Ltd, Edinburgh*) 24s net
- KLYNES, GEOFFREY, M D, F R C S, F R C O G *Ambroise Pare* (*Falcon Educational Books, London*) 15s net
- MONROE, ROBERT T, M D *Diseases in Old Age* (*Harvard University Press, Cambridge*) 32s 6d net
- MORISON, J EDGAR, M D, B SC *Foetal and Neonatal Pathology* (*Butterworth & Co (Publishers) Ltd, London*) 50s net
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ON OCCLUSION OF THE ABDOMINAL AORTA

By CATHERINE C BURT, B Sc, M B, Ch B, Sir JAMES LEARMONTH, K C V O, C B E, Ch M, F R C S E, and R L RICHARDS, M D, M R C P E

(From the Department of Surgery, University of Edinburgh)

PART III—AORTIC EMBOLISM

Clinical Observations

(a) MATERIAL

IN our series there were 16 patients who presented the clinical features of sudden occlusion of the aortic bifurcation (Table VII). In all the occlusion was due to embolism, although in 2 (Cases 7 and 8) the embolus itself did not occlude the bifurcation and the symptoms of aortic occlusion were probably produced by reflex vasospasm, in a third (Case 6) simultaneous embolism of both femoral arteries occurred. The ages of the patients ranged from 4 years to 82 years, and there were 5 males and 11 females. Eight (Cases 1, 7, 8, 9, 10, 12, 13 and 15) of the patients were suffering from rheumatic heart disease with auricular fibrillation, and the source of the embolus was presumed to be a thrombus in the left atrium, 3 patients (Cases 2, 4 and 6) were fibrillating but did not have rheumatic heart disease, in 1 patient (Case 3) the origin of the embolus was a mural thrombus in the left ventricle following a myocardial infarct, and in another (Case 5) the embolus originated in the calf veins and reached the arterial circulation through a patent foramen ovale. In 3 cases the occlusion occurred during the post-operative period, after ligation of the saphenous vein (Case 11), after salpingectomy (Case 14) and after appendicectomy (Case 16). The exact course of events leading to the lodgement of the aortic emboli in the last 3 cases is uncertain. In Cases 11 and 14 pulmonary embolism had occurred previous to the aortic occlusion and it is suggested that as a result of the pulmonary infarctions propagating thrombi formed in the pulmonary veins and were swept into the systemic circulation, alternatively the emboli may have been of the paradoxical type and have had their origin in the same veins as did the pulmonary emboli. In Case 16 the embolus probably came from the left ventricle.

In 9 of the 16 cases other embolic episodes occurred before and/or after the aortic occlusion (Table VII).

(b) THE CLINICAL PICTURE

The exact history and findings on examination depend upon the behaviour of the embolus. It may block first one common iliac artery and then the other, so that one limb is affected before the other, or it may be impacted more firmly into one common iliac artery so that the opposite limb still receives a trickle of blood. Occasionally a small embolus which is not large enough to obstruct the aortic bifurcation may produce a clinical picture which at first suggests aortic embolism;

TABLE VII
Aortic Embolism Details of Cases

Case	Sex	Age	Origin of Embolus	Other Emboli		Time Interval *	Treatment	Result
				Pre aortic	Post aortic			
1	F	58	Rheumatic carditis Auricular fibrillation	R femoral	Sup mesenteric L renal	7 days	Conservative Amp L leg	Died of mesenteric embolism 6 weeks later
2	F	76	Auricular fibrillation	—	—	5 days	Conservative	Died 3 months later,
3	M	57	Myocardial infarction	—	—	1½ hours	Bilat amp Nil	cardiac failure Died within 24 hours
4	F	53	Auricular fibrillation	—	—	48 hours	Conservative	Carcinoma recti
5	M	63	Paradoxical L calf veins	L cerebral R brachial	—	—	Nil	Died 3 weeks later
6	F	82	Auricular fibrillation	—	—	6 weeks	Nil	Died
7	M	56	Rheumatic carditis Auricular fibrillation	—	R cerebral	3 hours	Exploration of L popliteal artery	Autopsy diagnosis Died 2 weeks later Died of cerebral embolism 6 months later
8	F	40	Rheumatic carditis Auricular fibrillation	—	—	3½ hours	Conservative	Recovered
9	F	50	Rheumatic carditis Auricular fibrillation	Multiple vis ceral	—	11 hours	Embolectomy Amp R leg	Died 36 days later Moist gangrene
10	F	41	Rheumatic carditis Auricular fibrillation	—	—	18½ hours	R femoral em bolectomy	Died immediately post operatively
11	F	57	Post operative	R pulmonary	? cerebral	2 hours	Embolectomy	Alive and well 4½ years later
12	F	55	Rheumatic carditis Auricular fibrillation	—	R cerebral (2)	4 hours	Embolectomy	Immediate recovery Died 5½ months later of cerebral embolism
13	M	47	Rheumatic carditis Auricular fibrillation	—	—	5 hours	Embolectomy	Alive and well 18 months later
14	F	36	Post operative	L pulmonary x 3	—	9 hours	Embolectomy	Alive and well 5½ years later
15	F	42	Rheumatic carditis Auricular fibrillation	R ext iliac R popliteal	—	24 hours	Embolectomy	Died 36 hours later
16	M	4	Post operative	R renal L femoral R and L popliteal	—	15 hours	Embolectomy	Died 14 hours later

* Before patient seen in conservatively treated cases before embolectomy in operated cases

within an hour or two, however, it becomes apparent that recovery in one or both lower limbs is taking place

These points may be illustrated by considering in some detail the development of the clinical picture in our 16 cases. For descriptive purposes we have arbitrarily divided the course of events during the first three days after the lodgement of an aortic embolus into *the onset* and *three stages*, the first six hours, from six to forty-eight hours and from forty-eight to seventy-two hours

(1) *The Onset*—In 12 of the 16 cases accurate information is available about the initial symptoms. At the moment of onset, 9 patients were resting, either in a chair or in bed, the other 3 were standing.

One patient described a gradual onset, and one (a child) did not complain, the others gave a history of a sudden incident

Pain was the initial symptom in 8 cases, it was felt first in the legs in 4 cases, in the abdomen in 2 cases, in the lumbar region in one case and simultaneously in the lumbar region and in the legs in one case. Within a matter of minutes pain and loss of power in the legs became the most important features in all cases. The pain in the legs was described as cramp-like or "like a heavy weight" and was usually referred to the calf, that in the abdomen was also described as cramp-like. All 8 patients described the intensity of the pain as "severe". Three patients who did not experience pain as the initial symptom complained first of sudden loss of power in the lower limbs, 2 soon experienced pain in the legs but the other patient insisted that she had "no pain anywhere". Of the 3 patients who were standing at the time of onset, 2 would have fallen had they not been caught by a relative, the other collapsed and was unable to walk but crawled to a door and called for help.

In the majority of the cases symptoms appeared simultaneously in both lower limbs. One patient noted that the right foot was affected before the left, one hour before the major episode, another complained of cramp-like pain in the right calf, examination of the limb at that time did not reveal any vascular or neurological disturbance.

(11) *The First Six Hours*—Six of the patients were seen within six hours of their first symptoms, the clinical picture varied considerably. The most rapid development was seen in Case 11, within one and a half hours there was complete paralysis of the lower limbs, cyanosis extending to the inguinal ligament and sensory loss as high as the twelfth thoracic dermatome. As a contrast, in Case 12 at one and a half hours active flexion of the hip, knee and toes on both sides was possible, loss of sensation was confined to the foot and outer side of the leg and only the toes and distal portions of the feet were blanched, the legs were mottled in appearance and the thighs pink.

At four hours another patient with complete obstruction (Case 13) had paralysis below the knee on the right but on the left could plantar-flex the foot and had a flicker of voluntary power in the dorsiflexors of the ankle and in the long extensors of the toes. Sensory loss on the right extended to the level of the adductor tubercle, on the left to the neck of the fibula on the lateral side and to mid-leg on the medial side. Position sense was absent in all the joints of the toes and in both ankles. The feet were white and the toes had a shrivelled appearance, the legs were pale, the skin did not blanch on pressure and the superficial veins were not collapsed and filled slowly when emptied by pressure.

Two important observations were made on the 4 patients who presented signs of complete occlusion, (a) during the first six hours the joints remained mobile but not lax and in none of the cases were muscle contractures noted, and (b) in two cases at one and a half

and four hours the knee and ankle jerks were absent, in a third at one and a half hours the knee jerks were present but the ankle jerks absent, in the fourth the reflexes were not tested

During the first six hours 2 patients showed signs of spontaneous recovery and it became apparent that the original diagnosis of an embolus occluding the aortic bifurcation was incorrect

CASE 7—A man, aged 56, had suffered from rheumatic heart disease for many years and was fibrillating Three hours before admission he noted the

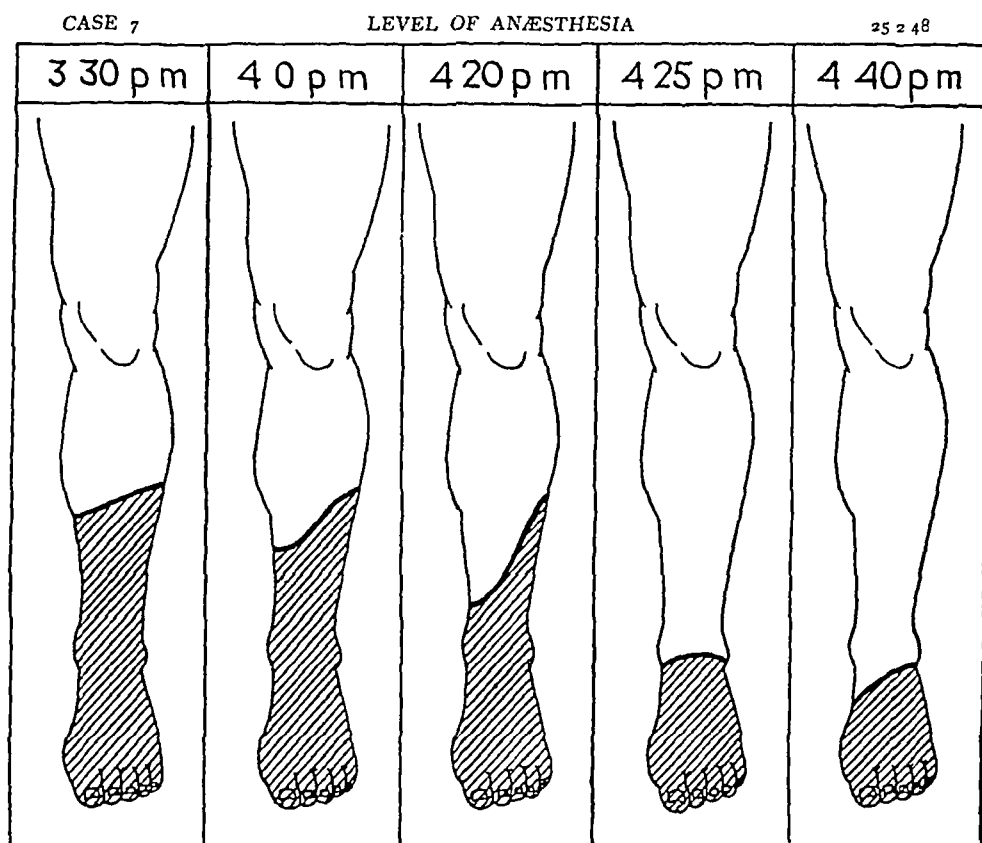
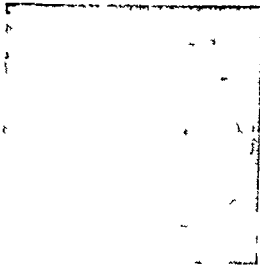


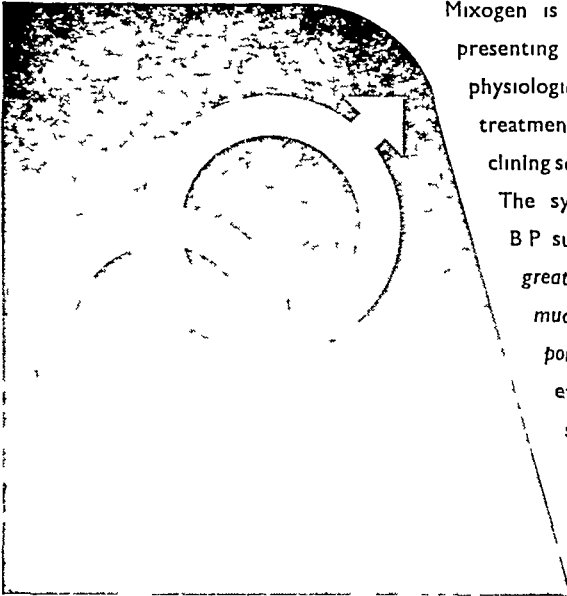
FIG 23—Aortic embolism CASE 7—To show the rapid regression of anæsthesia in aortic pseudo embolism

gradual onset of pain in both calves and slight pain in the lumbar region The pain in the legs increased in intensity and, after about ten minutes, he became conscious of numbness, tingling and loss of power in both legs, more marked in the left After thirty minutes the pain in the right leg subsided and he noted that he could move it better than the left, but he was unable to walk

On admission there was paralysis of the left leg distal to the knee and a level of analgesia 17 cm proximal to the medial malleolus There was no flexion contracture and the ankle jerk was present The foot was white, the leg cyanosed and the veins were empty The pulse could not be felt in the femoral artery On the right there was no motor paralysis, a strip of analgesia was present along the outer border of the foot and only the toes and distal



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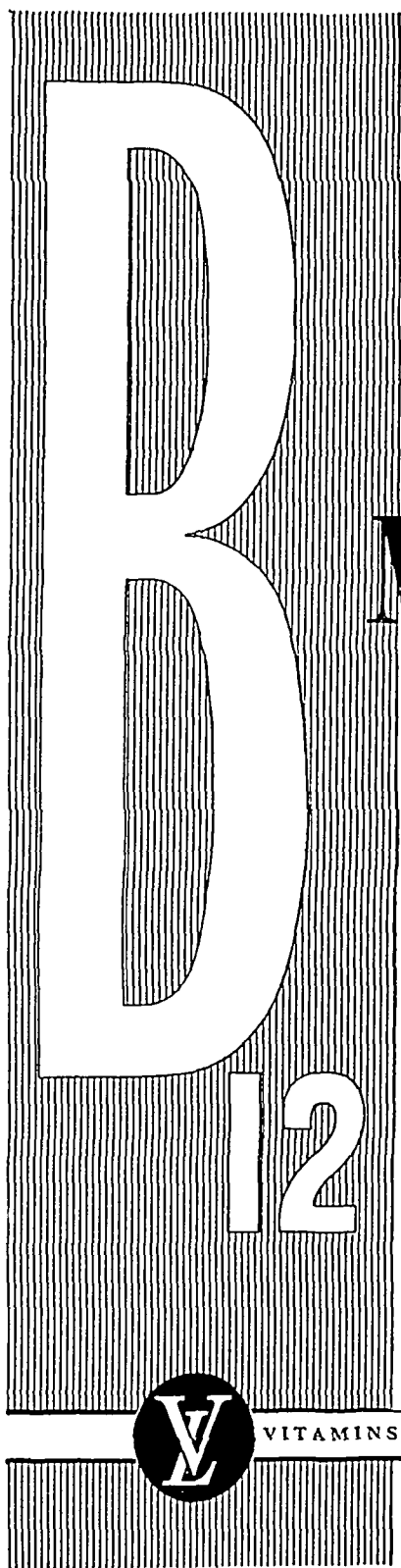


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third of the foot were blanched. Pulsation was felt in the right femoral artery. The right foot rapidly recovered. The left leg at first showed a tendency to improvement, recovery was noted in both the calf and dorsiflexors of the foot and the sensory level receded distally (Fig. 23). However, at six hours the calf muscle felt firm and was a little tender and the ankle jerk could not be elicited. Because of these findings it was considered probable that a small embolus had lodged in the left popliteal artery and this vessel was explored. It was found to be patent but not pulsating. When it was opened, blood flowed from the incision—at first dark and sluggish, but soon a brisk non-pulsatile stream of bright red blood. The artery was then opened distally and the origin of the anterior and posterior tibial arteries explored but an embolus was not found.

The patient recovered from this episode but died six months later of

TABLE VIII

Aortic Embolism State of Pulses in Cases Seen within Six Hours of Onset

Case	Time	Pulses								
		Aorta	External Iliac		Femoral		Popliteal		Posterior Tibial	
			Right	Left	Right	Left	Right	Left	Right	Left
3	1½ hr	Not felt	++	++	+	+	—	—	—	—
	9 hr	Not felt	—	—	—	—	—	—	—	—
7	3 hr	N R	N R	N R	+	—	—	—	—	—
8	3½ hr	N R	N R	N R	+	±	—	—	—	—
11	2 hr	N R	N R	N R	—	feeble	—	—	—	—
12	4 hr	N R	N R	N R	—	—	—	—	—	—
13	5 hr	++†	—	—	—	—	—	—	—	—

N R = Not recorded

* Left femoral artery palpable as thick non pulsatile cord

† Downward thrust Stops 5 cm. above umbilicus

cerebral embolism. At autopsy the aortic bifurcation was not occluded, unfortunately the vessels of the lower limbs were not examined.

CASE 8—A 40-year-old housewife who was known to have had rheumatic carditis since the age of 18 was admitted three and a half hours after she had suddenly experienced severe pain in both calves and loss of power in the legs.

When first seen, the right lower limb was normal apart from coldness of the foot and absent pulses in the popliteal, dorsalis pedis and posterior tibial arteries. On the left there was paralysis below the knee although a flicker of voluntary movement was seen in the calf, analgesia extended to knee level and the lower half of the leg and foot was white and cold. A femoral pulse was felt on both sides, more easily on the right. Progressive improvement occurred and at five hours both dorsiflexion and plantar flexion of the left foot and toe movements were present, analgesia was confined to the foot and the skin was pink at the ankle. Without operation complete recovery followed.

The state of the pulses in this group of cases is shown in Table VIII. One and a half hours after the first symptoms in Case 3 pulsation was

felt in the external iliac and femoral arteries, but in the latter the pulsation had a definite thrusting quality and it was considered that this represented a downward thrust transmitted from pulsation in the external iliac arteries. This view was supported by the fact that the left femoral artery could be felt as a firm rounded cord in the femoral triangle. Seven and a half hours later pulsation could no longer be felt in the external iliac arteries and it was then that the diagnosis of aortic occlusion was made. This patient had had a myocardial infarct and at autopsy a large loosely adherent mural thrombus was found in the left ventricle, multiple emboli probably originated from this thrombus. The significance of the pulsation in the femoral arteries in Cases 7 and 8 has already been considered. In Case 11 feeble pulsation was felt in the left femoral artery only, but in Cases 12 and 13 both femoral pulses were absent. In Case 13 pulsation of the aorta in the epigastrium was forcible and a very distinct downward thrust was felt which ceased 5 cm. above the umbilicus.

(11) *From Six to Forty-eight Hours*—Seven patients (Cases 3, 7, 8, 10, 14, 15 and 16) were first seen during this period or were followed through from the earlier period without embolectomy. We can exclude from further consideration those 2 patients (Cases 7 and 8) in whom at six hours it was already apparent that spontaneous improvement was occurring. In the remaining 5 cases the outstanding finding which was not observed in any case during the first six hours was the presence of contractures of the muscles of the calf, of the anterior tibial group of muscles, or of both. The contracture was noted in Case 3 at nine hours but was not recorded in Case 14 after the same time interval. In Case 10 at eighteen and a half hours a well-marked flexion contracture of both ankles was noted, and in Case 15 at twenty-four hours a similar contracture was present and the calf muscles were described as "doughy and slightly tender". Associated with these contractures the toe and ankle joints became stiff and the tendons of the contracted muscles stood out as tight, prominent cords. In general the extent of the motor and sensory paralysis was greater in this group than in the cases seen earlier. All these patients showed complete motor paralysis below the knees and a sensory level at or proximal to mid-thigh. Signs of gross impairment of the circulation to the lower limbs was present in all, but gangrene was not observed. However, in Case 3 at twenty-two hours commencing gangrene of the penis was noted.

The fifth case in which muscle contractures were noted presented certain unusual features —

CASE 16 (Mr F H Robarts's case)—A boy, aged 4 years, was operated on for acute appendicitis, a gangrenous appendix was removed and a small abscess overlying the right iliac vessels was drained. For the first forty-eight hours his progress was satisfactory but during the next twenty-four hours he vomited twice. At this time he appeared dehydrated and there was abdominal distension but he did not complain of pain. An intravenous saline infusion was given into the right long saphenous vein. On the evening of the third

post-operative day he became restless and restlessness continued through the night. The next morning his left leg was noted to be mottled, swollen and cold. On the afternoon of the fourth post-operative day, the findings were as follows —

The child was restless but did not complain of pain. During the examination he volunteered the information that his feet were "sore". There was paralysis of both lower limbs below the knee, voluntary activity was present in the thigh muscles on both sides, but accurate assessment of this could not be made. On the right a full range of passive movement was obtained at all joints, on the left flexion contractures were noted in the calf muscles and toe flexors and these muscles felt "doughy" but were not tender. Both knee and ankle jerks were absent and stimulation of the soles did not elicit any response in the great toes. The level of analgesia to pinprick was at the ankle on the right and at the knee on the left. The left leg was slightly swollen but the foot and toes had a shrivelled appearance, the right foot and leg were normal in this respect. The right foot was blanched and the veins were poorly filled, the left foot was pallid, the toes were cyanosed and the leg was mottled. Both limbs were cold, the right to mid-leg, the left to mid-thigh. Pulsation could not be felt in any vessel in either limb.

The time of onset in this case cannot be determined, but comparison of the findings with the clinical picture in the other cases leads us to conclude that the left leg had been ischæmic, certainly for more than six hours and probably for twelve hours.

During this period one patient (Case 10) showed evidence of some spontaneous recovery in the left leg, this was associated with return of the femoral pulse, regression of the sensory level and *almost complete disappearance* of the flexion contracture of the ankle.

(iv) *From Forty-eight to Seventy-two Hours* — Only one patient (Case 4) was observed during this stage. There were slight flexion contractures of the ankles but the toe joints were lax. Complete paralysis of the lower limbs was present and the sensory levels were at the junction of the middle and lower thirds of the thighs. Pulsation in the aorta was not felt, but the abdomen was distended. There was no palpable pulse in any of the arteries in the lower limbs. The feet and distal two-thirds of the legs were cyanosed and did not blanch on pressure. Proximal to this was a zone of livid red discolouration which did blanch on pressure. The feet and legs were slightly swollen.

(v) *Summary* — These three stages into which we have arbitrarily divided the clinical picture during the first seventy-two hours after an acute arterial occlusion are shown in Table IX. It must be stressed that the times at which one stage passes into the next are not fixed but vary from case to case and depend upon a number of factors such as the completeness of the block, the degree of reflex vasospasm and the rapidity with which a collateral circulation can develop. What we wish to emphasise is that, in the evolution of the clinical picture after an acute arterial occlusion, whether at the aortic bifurcation or in a more peripheral vessel, it is possible to recognise three distinct stages: an initial stage in which signs of paralysis develop but muscle contractures

are not observed or are minimal, a second stage in which muscle contractures develop, joints become stiff and tendons of contracted muscles stand out as firm cords, and, if the ischæmia persists, a third stage in which contractures disappear, the muscles soften, the joints become loose and the limb swells. If an accurate prognosis is to be given, it is important to recognise the stage that has been reached.

(c) THE COURSE OF EVENTS IN CASES NOT OPERATED UPON

Of the 16 cases, one-half did not have embolectomy performed. Of these 8 cases, 2 (Cases 7 and 8) recovered but in both the obstruction was

TABLE IX
Acute Total or Almost Total Ischæmia of Limb

Duration (hours)	Clinical Features	Prognosis
To 6	Motor and/or sensory palsy \pm Digits in flexion \pm Slight elastic resistance to passive extension	Complete or almost complete recovery
6-48	Motor and sensory palsy + Muscles firm/hard Digits stiff in flexion, ankle/wrist stiff, tendons tight prominent cords	<i>Early</i> —Complete or incomplete motor and sensory recovery Contracture and joint stiffness \pm <i>Late</i> —No recovery of power or of sensation—contracture (muscle fibrosis)—joint stiffness. Skin preserved—or tips of digits lost
48-72+	Motor and sensory palsy persist All joints lax—tendons no longer prominent Hard muscles soften gradually Limb swollen	Muscles dead, recovery not possible Fibrosis not possible Some skin may be preserved

not complete. One of these patients died later from a cerebral embolus (Case 7), the other is still alive but is severely crippled by her cardiac disease. The remaining 6 patients (Cases 1-6) died, and in all cases the aortic embolus undoubtedly contributed to the fatal outcome. In one of these patients the presence of an aortic embolus was not suspected before death, the remaining 5 patients died twenty-four hours, three weeks, six weeks, eight weeks and three months after the lodgement of the embolus. The case in which the presence of an aortic embolus was not suspected before death (Case 5) is of interest because it is the only case in the series in which infarction of the bowel occurred. The bifid embolus, which originated in the veins of the left calf and passed through a patent foramen ovale, lodged in the orifices of the coeliac axis and superior mesenteric arteries, and obstructed the inferior mesenteric artery (Fig 24) so that the intestines were suddenly completely deprived of blood. The patient who died within twenty-four hours (Case 3) did not develop gangrene of the lower limbs but signs of impending gangrene of the penis were noted before death. It is noteworthy that, shortly before he died, this patient passed urine which did not contain

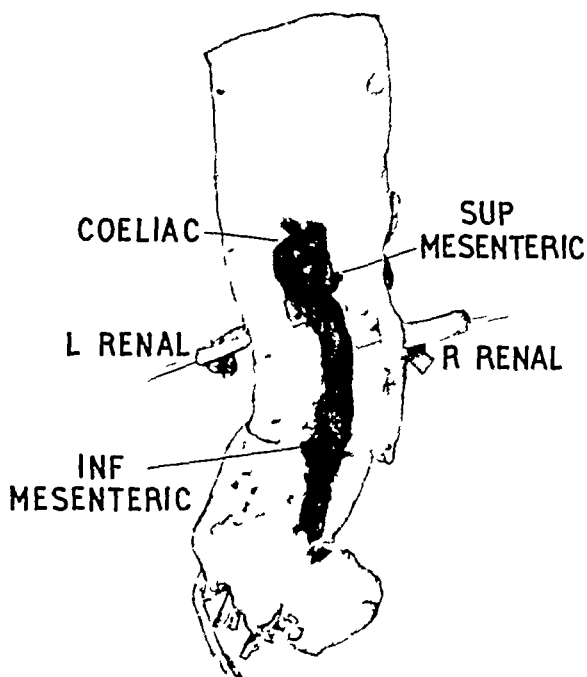


FIG 24 —Aortic embolism CASE 5 —To show occlusion of branches of aorta without complete occlusion of its lumen

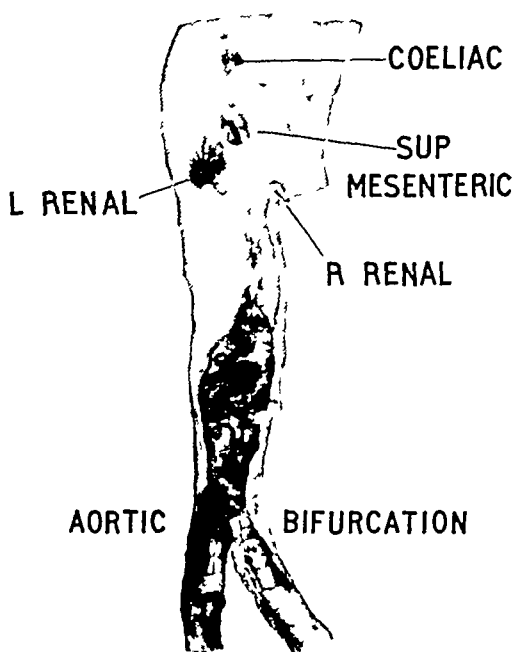


FIG 26 —Aortic embolism CASE 1 —To show extent of embolus and consecutive thrombus (Compare FIG 25)



FIG 27 —Aortic embolism CASE 2 —To show extent of gangrene in foot



FIG 28 —Aortic embolism CASE 6 —To show extent of gangrene in legs

blood At autopsy the thrombus occluding the aorta was found to extend as high as the origin of the renal arteries but, since the upper portion of the thrombus was conical in shape, the openings of these vessels were not occluded The pelvic colon, rectum and anus had been removed previously for carcinoma of the rectum The remaining segments of the intestine, and the bladder, were not ischæmic

Two of the 3 patients who survived for some weeks required ampu-

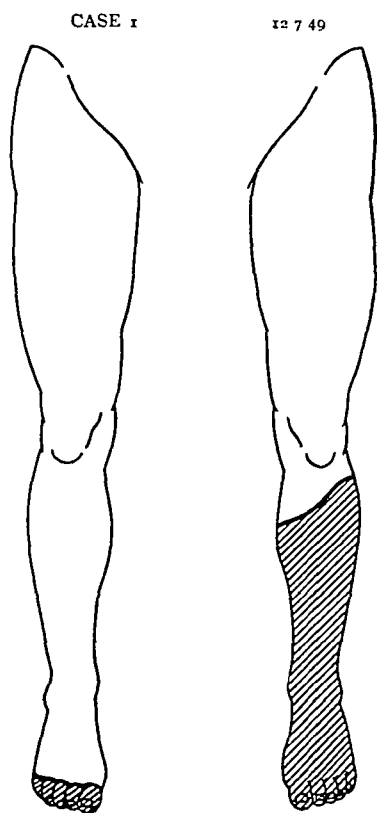


FIG 25 —Aortic embolism CASE 1 —To show sensory levels

tations, one of the left leg and the second of both legs, the third patient died of cardiac failure before amputation could be performed

CASE 1 —This patient was first seen seven days after the estimated time of lodgement of the embolus She gave a history indicating a previous embolic episode in the right lower limb seven months earlier The feet were held in plantar flexion and there was a slight flexion contracture of both ankles The toes were mobile On the left there was complete paralysis below the knee, and the calf was swollen, tense and acutely tender On the right there was voluntary power in the calf muscle, tibialis anterior and peronæi, but the long extensors of the toes and all the small muscles of the foot were paralysed The sensory level on the left was just below the knee (Fig 25), on the right only the toes were insensitive and pinprick on the sole produced a deep burning

sensation Sense of position was present in the joints of the right toes but was absent in those of the left toes, and in the left ankle unless the foot was dorsiflexed sufficiently to stretch the painful calf muscles The left foot and leg were blue, cold and swollen, the veins were empty and there had been extravasation of blood into the tissues On the right the toes were cyanosed but there was a small blistered area on the dorsum of the foot The aorta could be felt pulsating strongly at the level of the umbilicus, but distal to this the only pulse felt was a faint right femoral

The condition of the left leg did not improve and two weeks later a guillotine amputation at mid-thigh was performed The right leg improved at first, but after the amputation of the left leg its condition deteriorated slowly and amputation of the second limb would probably have been required if the patient had not died suddenly with symptoms suggesting a mesenteric embolus This diagnosis was confirmed at autopsy, recent emboli were found in the superior mesenteric and left renal arteries, and the coeliac axis and aortic bifurcation were both occluded by older emboli (Fig 26)

CASE 2 —This elderly lady was seen five days after the lodgement of an embolus At this time there was evidence of a complete aortic block, as judged by absence of both femoral pulses The degree of paralysis was greater on the left side than on the right, on the left the ankle and toes were quite lax, on the right flexion contracture of the calf muscles was present She was treated with anticoagulants Only the feet became gangrenous (Fig 27) and amputations had to be performed on the right at sixty days and on the left five days later Her condition gradually deteriorated after the second amputation and she died seventy-eight days after her embolism At autopsy "the aorta was plugged by old, brown, tough ante-mortem thrombus," which extended into both common iliac arteries The femoral arteries were occluded by thrombi which were considered to be of more recent origin than the thrombus in the aorta and iliac vessels

CASE 6 —One morning, on rising, a lady of 80 had a sudden feeling of giddiness followed by loss of power in both legs Six weeks after this episode there was dry gangrene of the feet and moist gangrene of the distal two-thirds of both legs (Fig 28) Faint pulsation could be felt in the proximal part of Scarpa's triangle Auricular fibrillation had been present for some weeks, it was thought probable that a "saddle embolus" had split at the aortic bifurcation and that portions of it had been swept into both popliteal or common femoral arteries The patient's general condition never permitted amputation and she died fourteen days later At autopsy the heart was found to be dilated and the coronary arteries were atheromatous The myocardium was healthy and none of the chambers contained ante-mortem thrombus The aorta was atheromatous and organised thrombus was adherent to a plaque a few centimetres above the bifurcation Both femoral arteries and the right profunda femoris artery were blocked by ante-mortem thrombus, the femoral veins were also thrombosed

(d) THE COURSE OF EVENTS AFTER EMBOLECTOMY

Eight patients were operated upon in an attempt to remove the occluding embolus In 4 cases the operation was unsuccessful —

CASE 9 (Mr F E Jardine's case) —Eleven hours after the initial symptom, operation was performed by Mr A R Murray. The embolus was removed piece-meal through incisions made in both femoral arteries in the femoral triangles. Although full circulation to the lower limbs appeared to be re-established at the end of the operation, the left lower limb did not recover and had to be amputated thirty-two days later. The vessels at the amputation site were thrombosed. A rapid, spreading moist gangrene of the stump developed and the patient died four days later. At autopsy a large, partially organised clot straddling the bifurcation of the aorta was found. On the right the thrombus extended to the bifurcation of the common iliac artery, but distal to that level the arteries were patent. On the left recent clot occluded the iliac and femoral arteries to the level of the amputation.

CASE 10 was operated upon eighteen and a half hours after the onset. Although the initial symptoms and signs were those of an aortic embolus, there were signs of recovery on the left side. As the patient's general condition was poor, a decision was made to explore the right femoral artery. Portions of recent red clot were removed from this artery but a free flow of blood was not obtained. It was thought that a block must be present more proximally but before any operative treatment for this was possible, the patient's condition rapidly deteriorated and she died as the incision in the thigh was being closed. An autopsy was not obtained.

CASE 15 —Operation at twenty-four hours. The aortic bifurcation was exposed by a transperitoneal approach and the embolus removed through an incision in the right common iliac artery. At the conclusion of the operation pulsation was felt in the left femoral artery but not in the right. The patient did not speak after the operation, although she ate and drank, and thirty-six hours later she died. During the post-operative period the contractures in the calf muscles and toe flexors became more severe (Table XI) and there was no evidence of sensory or motor recovery in either lower limb.

At autopsy it was found that the whole of the aortic embolus had been removed. Old emboli were found in the right external iliac artery and in the right femoral artery. There was a recent thrombus in the left popliteal artery (Fig. 29) and embolism of both anterior cerebral arteries.

CASE 16 —The interval between lodgement of the embolus and operation in this case cannot be estimated accurately but we consider that it was about fifteen hours. A transperitoneal approach was used and portions of clot were removed through incisions made in both common iliac arteries (Fig. 30). At the end of the operation a free flow of blood was not obtained, and pulsation was not felt in either external iliac or femoral artery. After the operation the child lived for only fourteen hours. During this period contractures developed in the calf muscles and toe flexors on the right, and the contractures on the left became more severe (Table XI). No motor or sensory recovery was noted in either limb.

At autopsy the aorta was found to be blocked by clot for 3 cm proximal to the bifurcation (Fig. 31). The upper 1 cm of this clot was white and firm, and not adherent to the wall, the distal 2 cm were softer, red and slightly adherent. Proximally a thin thread of soft red clot extended to the level of the renal arteries. Distally the right common iliac artery was filled with old non-adherent white thrombus and a strip of recent red clot was adherent to the anterior wall of the left common iliac artery. The left femoral artery

was blocked at the origin of the profunda by old, firm, non-adherent white clot and both popliteal arteries were occluded by softer red clot. The coeliac, superior mesenteric and renal arteries were patent but the right kidney contained numerous infarcts. The inferior mesenteric artery was blocked by clot as far as it was followed (2 cm). The femoral veins, the iliac veins and the inferior vena cava were patent, with normal endothelium. The small residual abscess overlying the right common iliac vessels had not caused any macroscopic

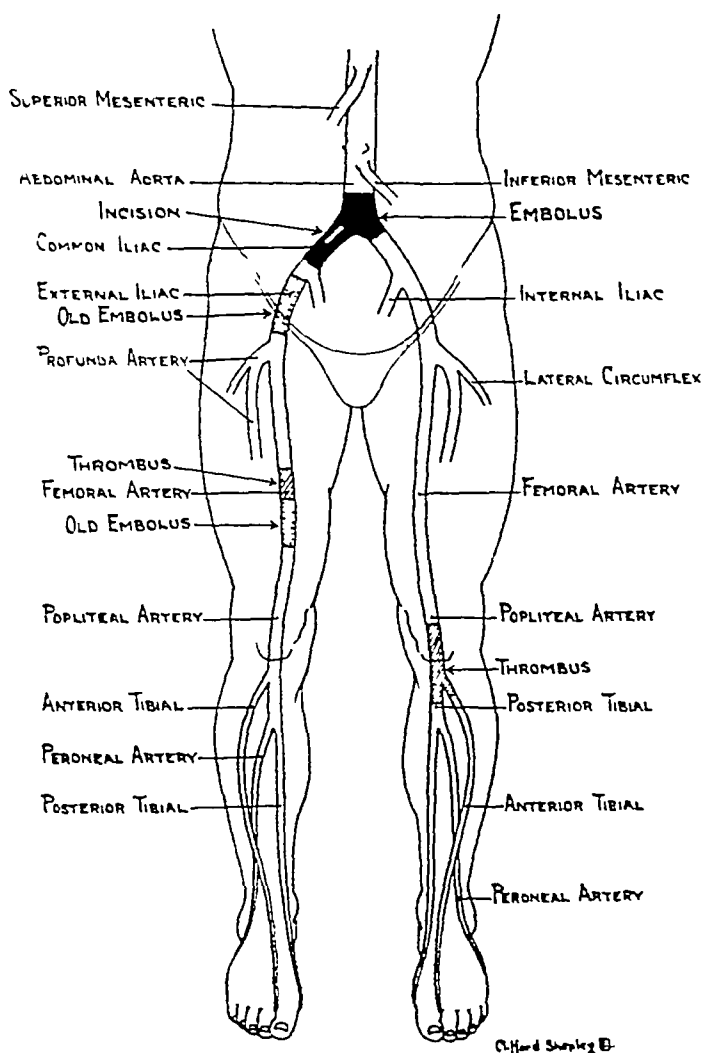


FIG 29—Aortic embolism CASE 15—To show extent of recent and old arterial blockage

inflammatory change in the vessel walls. The pulmonary artery and its primary branches were healthy and did not contain thrombus nor was there any evidence of pulmonary infarction. The heart did not show any developmental anomaly. The valves were healthy and the only possible source of an embolus was a small area of roughened endocardium on the septal wall of the left ventricle overlying several small sub-endocardial hæmorrhages. Two small fragments of ante-mortem clot were lying free in the cavity of the left ventricle.

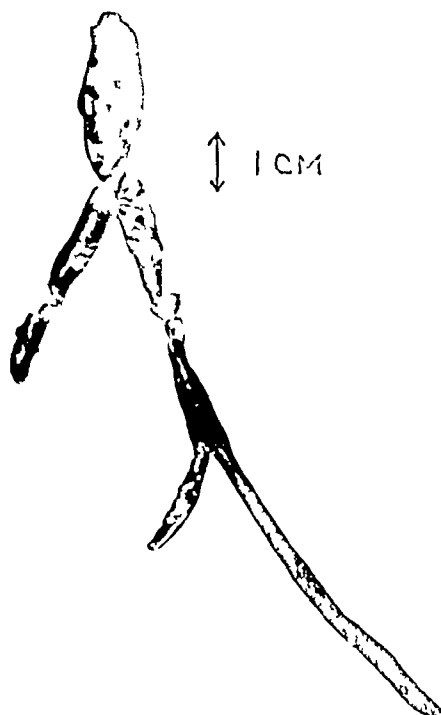


FIG 30—Aortic embolism CASE 16—To show embolus and consecutive thrombus removed at aortic embolectomy

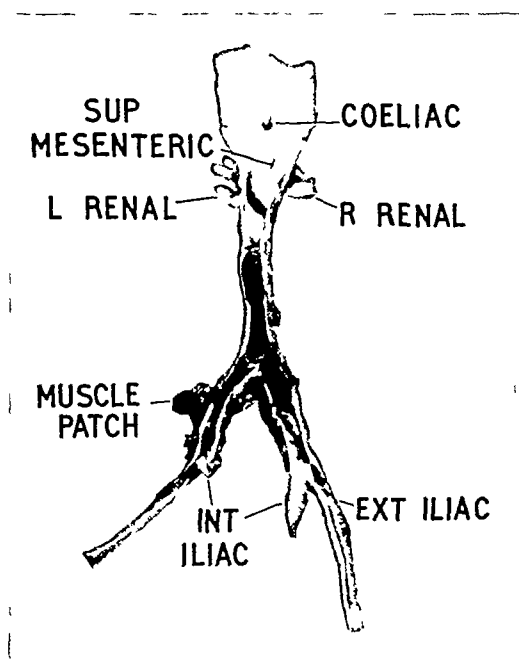


FIG 31—Aortic embolism CASE 16—To show aorta at autopsy with further embolism and consecutive thrombosis (Compare Fig 30)



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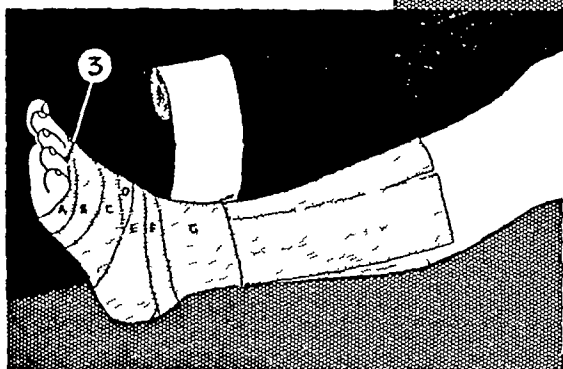
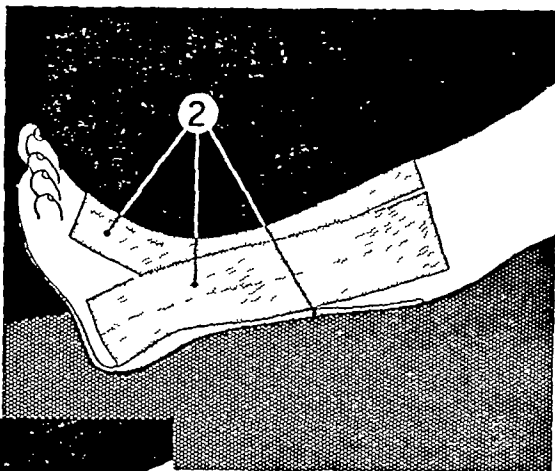
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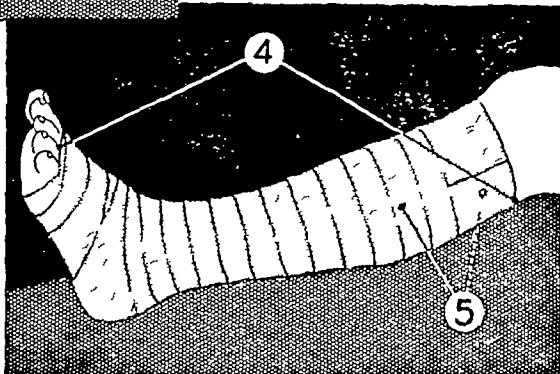
4 Leg should be covered from webs of toes to a point just below the bend of the knee

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The course of events in the 4 successful cases (Cases 11-14) is shown in Fig 32 and Tables X-XIV These patients were operated upon

TABLE X

Aortic Embolectomy Time of Return of Peripheral Pulses after Operation

Case	Leg	Femoral	Popliteal	Posterior Tibial	Dorsalis Pedis	Perforating Peroneal
11	R	Immediately	3 weeks	11 months	1 month	—
	L	Immediately	3 weeks	11 months	1 month	—
12	R	? Immediately	? 5 hours	5 hours	5 hours	7 days
	L	? Immediately	—	1½ months	—	—
13	R	Immediately	? 1 week	18 days	3 months	—
	L	Immediately	1 week	? 24 hours *	1 week	3 months
14	R	Immediately	48 hours	19 days	12 months	—
	L	Immediately	—	Immediately	2 hours	—

* Absent at three months

TABLE XI

Aortic Embolectomy Contractures

Case	Time After Lodgement (hours)	Limb	Pre operative		Immediate Post operative		Post operative Recovery	
			Calf Muscle	Toe Flexors	Calf Muscle	Toe Flexors	Calf Muscle	Toe Flexors
11	2	R	—	—	±	—	24 hours	
		L	—	—	—	—	1 month	
12	4	R	—	—	—	—		
		L	—	—	±	—	10 hours	
13	5	R	—	—	—	—		
		L	—	—	—	—		
14	9	R	—	—	—	—		
		L	—	—	—	—		
15	24	R	+	+	++	++	No recovery Patient died 36 hours after operation	
		L	+	+	++	++		
16	? 15	R	±	—	+	+	Patient died 14 hours after operation	
		L	+	+	+	+		

TABLE XII

Aortic Embolectomy Power of Muscles

Case	Time After Lodgement (hours)	Limb	Pre operative Paralysis	Post operative Recovery Time				
				Thigh	Calf	Tibialis Anterior	Toe Flexors Extensors and Peronei	Small Muscles of Foot
11	2	R	Whole limb	9 hr	9 hr	9 hr	30 hr	2½ mth
		L	Whole limb	9 hr	30 hr	30 hr	1 week	2½ mth
12	4	R	Dorsiflexors of foot *			9 hr	9 hr	12 hr
		L	Below knee *		9 hr	9 hr	12 hr	2½ mth
13	5	R	Below knee *		36 hr	36 hr	Extensors 36 hr Flexors 14 days	14 days
		L	Small muscles foot †			18 hr	18 hr	36 hr
14	9	R	Whole limb	8 hr	8 hr	8 hr	8 hr	1 mth
		L	Whole limb	8 hr	8 hr	8 hr	8 hr	3 wk

* Paresis thigh

† Paresis thigh and dorsiflexors foot and toes

TABLE XIII
Reflexes after Aortic Embolectomy

Case	Reflex		Weeks after Embolectomy						Months after Embolectomy					
			0 2	2 4	4 6	6 8	8 12	12 16	16 26	6 12	12 18	18 24	24 +	
11	K J	R			+		+	+		+	±		+	
		L			—		?	?		±	±		+	
	A J	R			—		+	+		+	±		+	
		L			—		—	±		+	±		+	
	Plantar	R			↓		↓	↓		+	↓		↓	
		L			0		0	0		↓	↓		↓	
	12	K J	R	+	±	+		+	++	Died at 5 months				
			L	+	—	+		±	++					
A J		R	—	—	—		+	++						
		L	—	—	—		—	±						
	Plantar	R	0	N R	N R		↓	?						
		L	0	N R	N R		↓	?						
	13	K J	R	—	—	—		—			—			
			L	—	+	+		+			+			
A J		R	—	—	—		±			±				
		L	—	—	—		+			+				
	Plantar	R	±	±	+		+			+				
		L	0	↓	↓		↓			↓				
	14	K J	R		N R					++				+
			L		N R					+		+		+
A J		R		—					—		±		+	
		L		+					+		+		+	
	Plantar	R		N R					↓		↓		↓	
		L		N R					↓		↓		↓	

A blank column indicates that no observations were made during that period

N R = No record ? = Doubtful response

Knee and Ankle Jerks — + = Normal reflex, ++ = Very brisk reflex, ± = diminished reflex, — = Absent reflex

Plantar — ↓ = Flexor response, o = No response

TABLE XIV
Aortic Embolectomy Vasomotor Studies

Case	Room Temperature °C	Limb	Toe Temperature in °C		Foot Blood Flow in ml/100 c.c./min		Oscillography Ankle Maximum	Time After Operation
			Average Resting	Maximum	Average Resting	Maximum		
11	18 o	L	24.3	N R	6.7	13.0	2.2	3½ yr
		R	24.0	N R	4.7	11.4	2.2	
12	15.5 18 o	L	15.5	N R	1.6	3.7*		1.3 mth
		R	15.5	N R	1.7	4.8*		
13	20 o	L	21.0	29.9†	1.0	N R	1.5	3 mth
		R	23.0	30.25†	1.3	N R	2.0	
14	22 o	L	25.8	32.2‡	13.5	17.0‡	3.5	4½ yr
		R	25.3	31.9‡	18.9	27.0‡	3.0	
Control (5) §	16 o 20.5	Average Range	23.2	33.3	3.6	20.9	3.1	
			20.1-30.0	30.5-35.0	1.5-7.0	13.0-30.8	1.8-4.0	

* Reactive hyperaemia water in plethysmograph at 40° C

† Feet covered with a blanket

‡ Spontaneous vasodilatation while feet were exposed

§ Normal subjects with normal peripheral pulses

within ten hours of their initial symptom. In 3 cases the aortic bifurcation was exposed by a transperitoneal approach and the clot removed through either one or both common iliac arteries. In the fourth (Case 14) a bilateral transfemoral approach was used but the embolus was not successfully removed until the aorta had been exposed and the clot "milked" down into the femoral arteries.

AORTIC EMBOLECTOMY—SENSATION

CASE NO	TIME IN HR AFTER LODGEMENT	PRE-OPERATIVE LEVEL	POST-OPERATIVE		RECOVERY			
			0-24 HOURS	1-7 DAYS	UNDER 1 MONTH	UNDER 6 MONTHS	UNDER 12 MONTHS	12-18 MONTHS
11	2							
12	4					DIED		
13	5							
14	9							

FIG 32—Aortic embolism CASES 11-14—Recovery of sensation after aortic embolectomy

The return of the circulation to the lower limbs may be considered first. At the conclusion of the operation in all 4 cases pulsation was present in both femoral arteries. Despite this, the circulation to the limbs returned very gradually and in the majority of the cases forty-eight hours elapsed before the colour and temperature of the feet could be regarded as satisfactory. This gradual return of the circulation is reflected in the delay that was observed in the return of the peripheral pulses (Table X). It will be noted that with the exception of Cases 12 and 14 in which the right and left posterior tibial and dorsalis pedis pulses respectively returned within a few hours, a delay of at least seven days occurred before the peripheral pulses returned.

In these 4 cases further studies of the circulation in the lower limbs were made by instrumental methods. Skin temperature of the toes and blood flow in the feet were measured with copper-constantan thermocouples and venous occlusion plethysmographs respectively, before and after inhibition of vasoconstrictor tone, in 3 of these patients pulsation at the ankle was measured with an oscillometer (Table XIV)

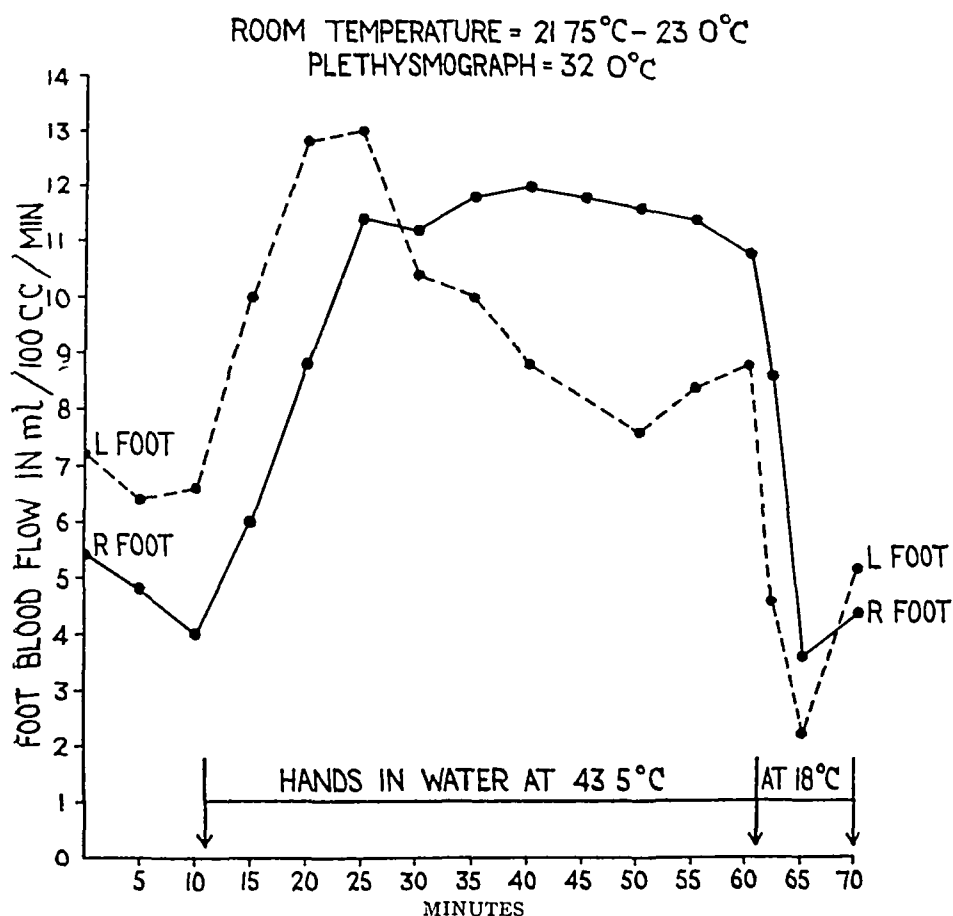


FIG 33 —Aortic embolism CASE 11 —Reflex vasodilatation test eleven months after aortic embolectomy

Little importance can be attached to the resting temperature of the toes and blood flow in the feet (Table XIV) as these vary greatly according to (1) the inherent vasoconstrictor tone of the individual, and (2) the environmental temperature, but it can be said that they did not differ significantly from normal

The maximum values of skin temperature or blood flow obtained when vasoconstrictor tone is inhibited give a measure of the vascular reserve in a limb (Table XIV). In Case 14 the temperature of the toes, blood flow in the feet and oscillometric readings indicated a normal circulation in both lower limbs with a reserve as great as that in the control subjects, this patient is able to walk several miles without pain. In Case 12 the maximum blood flow in the feet obtained by a com-

bination of indirect heating and direct heating was lower than normal. The patient, however, was 55 years old and had suffered from auricular fibrillation for some years, it is not known whether vasomotor function in the lower limbs was normal before lodgement of the aortic embolus. In Cases 11 (Fig 33) and 13 the maximum temperature of the toes and maximum blood flow in the feet were slightly below normal level in one limb and normal in the other, oscillometric readings were normal in Case 11 and only slightly below the normal range in one limb in Case 13.

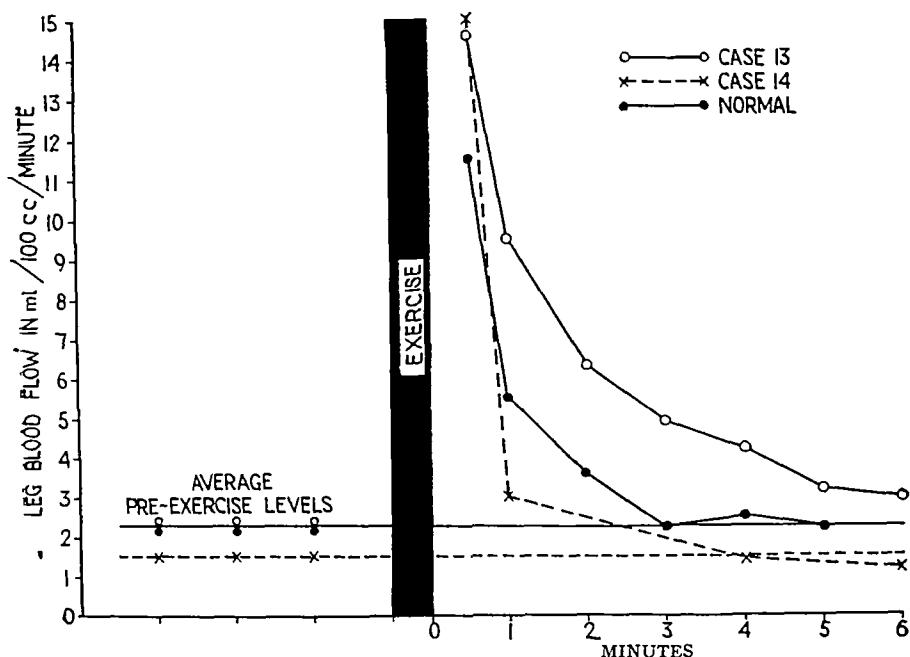


FIG 34—Aortic embolism CASES 13 and 14—Leg blood flow before and after exercise three months and twenty seven months respectively after aortic embolectomy

In 3 cases blood flow in the legs was recorded by a light celluloid plethysmograph before and after a period of exercise. In comparison with similar readings in control subjects, one of the patients tested (Case 14) had a normal response (Fig 34). In the other 2 cases (Case 11, Fig 35, and Case 13, Fig 34), return of the blood flow to the pre-exercise level was delayed, a finding similar to that observed in cases of obliterative arterial disease with intermittent claudication (Shepherd, 1950, Burt, unpublished observations). In neither case did the patient complain of pain during the test, but one of the patients (Case 11) states that, after walking for one mile uphill, she has to slow down because of pain in the calves, the other can walk two to three miles without difficulty.

The course of recovery from the neurological disturbances has also been studied in some detail. In a previous section we drew attention

to the significance of the development of muscle contractures in those cases in which ischæmia had been present for more than six hours. In none of the successful cases was a contracture noted before operation. In Case 11 flexion contracture of both ankles, more marked on the left, was first noted after the operation, that on the right disappeared within twenty-four hours but on the left the contracture persisted for a

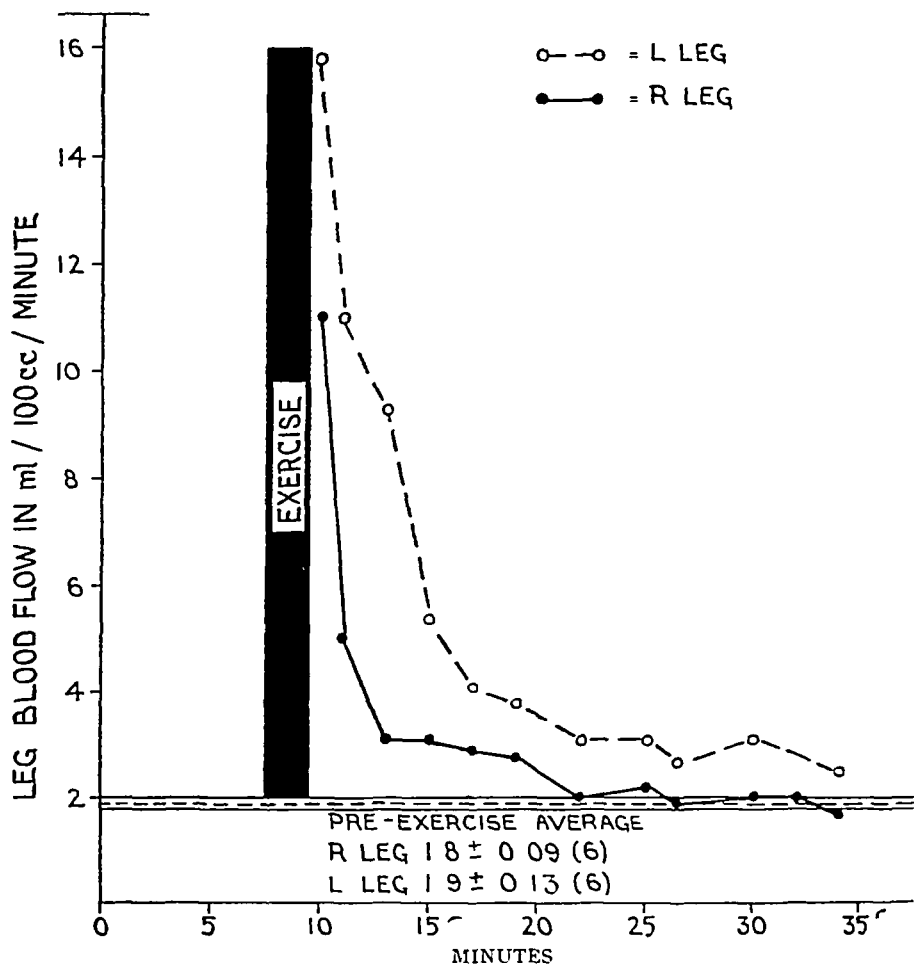


FIG 35 —Aortic embolism CASE 11 —Leg blood flow before and after exercise seventeen months after aortic embolectomy

month. In Case 12 slight contracture of the left ankle was present for ten hours after the operation.

The recovery of motor power in the limbs is shown in Table XII. It will be noted that the thigh muscles recovered within nine hours, but that recovery in the calf muscle and tibialis anterior was delayed up to thirty hours in 2 cases, and that in 2 cases the long muscles to the toes did not recover for seven to fourteen days. Assessment of function in the small muscles of the foot is often difficult, but our observations suggest that recovery in these muscles is often delayed for several weeks.

Tendon reflexes are later in returning than is voluntary power

(Table XIII) The earliest return of a knee jerk which was absent before operation was after eighteen days (Case 13, left), but this patient's ankle jerk on the same side returned after three days. Delays of up to eight months before recovery of the knee jerk and twelve months in the case of the ankle jerk, were recorded. The plantar response was also lost in most cases and was noted to return after an interval which varied from seven days to eleven months.

The recovery of sensation is illustrated in Fig. 32. Three of the patients had an area of sensory loss which persisted for more than twenty-four hours. Case 14 had a "stocking" area of anaesthesia on the right side which gradually receded and had disappeared in twelve months. The other 2 patients (Cases 11 and 13) had a different distribution of sensory loss and the residual neurological disturbance in these 2 cases approximately three months after operation requires consideration in some detail.

CASE 11—Embolectomy performed on 10.7.47. Examination of lower limbs on 28.9.47. "The left foot is held slightly inverted, the right foot appears normal. A full range of movement is possible at all joints. The left leg is wasted compared with the right, measurement reveals 1.5 cm. difference between the two calves. Power for all movements is good on the right, on the left there is a general slight weakness of all muscles below the knee with a specific weakness of the peronæi, long flexors of the toes and extensor digitorum brevis. The right knee jerk and ankle jerk are brisk, on the left the knee jerk is doubtfully present and the ankle jerk absent. On the right all modalities of sensation are normal. On the left there is an area of anaesthesia and analgesia on the inner side of the leg (see Fig. 32). Over the outer side of the leg and dorsum of foot, touch and pain are appreciated but localisation is faulty. On the sole the response to pinprick is delayed and unpleasant. Position sense in the toes is poor, but vibration sense is normal. The colour, temperature and nutrition of the feet are normal. The left dorsalis pedis is the only pulse felt in either foot."

CASE 13—Embolectomy on 16.5.50. Examination on 10.8.50. "The attitude of the feet is normal. A full range of movement is possible at all joints. The right thigh appears wasted compared with the left and measurement reveals 1 cm. difference between the two. Fasciculation is present in the right quadriceps and calf. Power is good in all muscles of both lower limbs, but both quadriceps are slightly weak. The right knee jerk is absent and the left knee jerk and both ankle jerks are present. Both plantar responses are flexor. On the right side there is a large area of hypæsthesia and hypalgesia over the medial aspect of the thigh and leg (Fig. 32). The right sole is slightly hyperæsthetic. Elsewhere response to pain and touch is normal. Position sense is normal in the toes, but vibration sense is absent over the right foot, medial malleolus and tibial tuberosity. There is no apparent vascular disturbance in either foot, on the right a good pulse is present in the posterior tibial and dorsalis pedis arteries, on the left only that in the dorsalis pedis is palpable."

The significance of these neurological disturbances will be considered later.

The late results in these four successful cases were as follows —

CASE 11 — This patient is alive and well four and a half years after embolectomy. She has a minimal residual weakness of the left foot.

CASE 12 — This patient made an excellent recovery from aortic embolectomy but died five and a half months later from a cerebral embolus. At autopsy the bifurcation of the aorta was found to be free from thrombus (Fig 36), and the suture line in the right common iliac artery was covered with endothelium.

CASE 13 — This patient made a successful recovery from the embolectomy and ten weeks later Mr Andrew Logan removed his left auricular appendix to minimise the possibility of further embolic episodes. During this operation a clot was expressed from the atrium. The histological appearance of this indicated that it was a few days old. The patient is alive and well eighteen months after embolectomy.

CASE 14 — This patient is alive and well five and a half years after embolectomy. Two years after the incident she was successfully delivered of a healthy child by Cæsarean section.

DISCUSSION

Although numerically small, this group of cases of sudden occlusion of the abdominal aorta is comparable with most of the larger collected series.

There is lack of unanimity regarding the sex incidence of aortic embolism. Of Welch's (1910) 59 cases, 30 were females, on the other hand, Hesse (1921) found that aortic embolism was commoner in men, while both Rothstein (1935) and Greenfield (1943) state that the incidence is equal in males and females. The preponderance of female patients in the present series is probably fortuitous although there is some evidence that in general embolic episodes occur more often in women than in men (Bull, 1922).

Aortic embolism is rare in infancy and childhood. Rothstein (1935) collected 11 cases from the literature and added a twelfth, of these, 7 were in infants in the first year of life, and 3 in children aged 12 years. The ages of the other 2 children were 3 and 3½ years, these were recorded by Allibert in 1828 (see Introduction). Few clinical details about these cases are available, even the sex of the children is not mentioned. In neither case was the source of an embolus found and in both cases the aorta was the only artery occluded. As Allibert's report antedated by some twenty years Virchow's exposition of the doctrine of embolism, these 2 cases may have been instances of thrombosis rather than embolism, indeed they are so regarded by Welch (1910). In our case (Case 16), the occlusion was considered to be due to an embolus, although the source of the embolus is uncertain, the other embolus in the left femoral artery, the infarcts in the right kidney and the fragments of ante-mortem clot in the left ventricle were sufficient evidence on which to make the diagnosis.

The high proportion of cases in which the embolus originated in the

heart (12 out of 16) and the frequency with which rheumatic carditis with auricular fibrillation was the pre-existing disease, are both observations which have been made by all who have examined the subject of aortic embolism. The finding that other embolic episodes occurred in more than half of the cases is to be expected, if a patient with heart disease survives after an aortic embolism, it is the rule rather than the exception for him to die within a relatively short time, from the effects of a further embolic episode. Since the source of the majority of emboli in cases of auricular fibrillation is the left auricular appendix, there is much to be said for the removal of the auricle in such a case, as was done in Case 13. So far as we are aware, he is the first recorded patient who has survived both aortic embolectomy and auriculectomy, a patient reported by Madden (1949) survived the embolectomy but died nine days after auriculectomy. Although removal of the auricle may prevent further embolic episodes, there is some doubt whether in cases of mitral stenosis an embolus which occludes the aortic bifurcation ever originates in the left auricle. *Welch (1910) pointed out that it is often difficult to believe that an embolus large enough to occlude the bifurcation could have passed through the extremely stenosed mitral valve which is found at autopsy.* This problem is illustrated by Case 12, the embolus removed at operation is shown in Fig 37, and when the patient died five months later the pathologist found the mitral valve "greatly thickened and narrowed so as to admit only the tip of the little finger". Mural thrombi in the ventricles are found at autopsy in approximately 13 per cent of cases of rheumatic heart disease (Garvin, 1941) and it seems reasonable to assume that the left ventricle may be a source of emboli which occlude the aortic bifurcation.

The 2 cases in which the symptoms of aortic embolism were temporarily produced by emboli which apparently lodged in relatively small vessels of the lower limbs are of great interest. Similar cases have been reported by Atlas (1942) and by Reynolds and Jirka (1944). There are two possible mechanisms which might produce this effect. First, an embolism might temporarily occlude the aortic bifurcation and then slip down into one or other iliac artery and thence into an artery in the pelvis or lower limb. Murray (1943) states, "In a fair proportion of these cases the immediate signs and symptoms suggest complete obstruction but under observation for a few hours the findings change, indicating that what was originally an impaction at the bifurcation of the aorta has changed, by the mass or masses, breaking and slipping down one or both sides to a lower level". An embolus which is large enough to do this could not be driven into such small vessels as the anterior and posterior tibial arteries. It is, however, conceivable that in some of these cases the major portion of the embolus slips into an internal iliac artery where its presence cannot be detected, and only a fragment passes into the vessels of a lower limb. The alternative explanation is that the embolus never lodges at the aortic bifurcation but when it impacts in a peripheral artery an intense degree of vaso-

spasm is provoked which extends as high as the iliac vessels. This is the view favoured by Atlas (1942). If we accept this hypothesis, however, we must explain why bilateral symptoms are not produced in every case of embolism of the vessels of a lower limb. Perhaps the effect is produced only when an embolus fragments in such a way that embolic episodes occur simultaneously in both lower limbs (*e.g.* Case 6). Another tentative explanation for this interesting phenomenon is that it may be produced by a small embolus which lodges in a small artery near the bifurcation of the aorta, such as the median sacral artery, with the result that both common iliac and both external iliac arteries are thrown into intense reflex spasm (Learmonth, 1948).

The sudden onset, with pain as the main symptom in the majority of cases, is typical. The cause of the pain in cases of arterial embolism is a subject which has been much discussed. Most authors have assumed that the sudden onset of pain indicates the moment of lodgement of the embolus and have attributed the pain to the impact of the embolus upon the arterial wall (Danzis, 1933) or to arterial spasm (McKechnie and Allen, 1936). As the late Sir Thomas Lewis (1936*a*) pointed out, it is difficult to believe that the lodgement of a clot which is soft and has approximately the same specific gravity as blood can have any pronounced physical effect upon the vessel wall. On the other hand, when embolectomy is performed it is often found that at the site of impaction of the embolus the artery is visibly distended and its wall slightly oedematous. This was observed in 2 of our 4 cases (Cases 12 and 15). Distension and oedema are probably not produced by the lodgement of the embolus but are due to the continuous hammering effect of cardiac systole upon the impacted embolus. Although this might appear to provide a satisfactory explanation for the pain of embolism, it must be admitted that experimental observations indicate that distension of an artery does not cause pain (Moore and Moore, 1933). In many cases the lodgement of an embolus is associated with a marked degree of reflex vasospasm, the 2 cases discussed above are examples of this phenomenon. There is, however, no good evidence that arterial spasm is of itself a painful condition.

Lewis (1936*a*) has pointed out that in cases of embolism pain occurs only when the part of the body which is made ischaemic contains muscular tissue, infarction of the brain, spleen and lungs* is usually painless whereas infarction of the heart, intestines or limbs is almost invariably associated with pain. He held that the pain of embolism is not felt at the site of lodgement of the embolus but always distal to that point, and that it is usually referred to a muscular portion of the limbs. Not all authorities are in agreement with Lewis on this point. For example, in a recent review Haimovici (1950) states, "The initial site of pain seems to be the region of lodgment of the embolus. Its maximal severity at the onset is usually located at the level of the occlusion and much less often in the distal part of the affected limb."

* Unless the infarct involves the pleural surface

In Lewis's opinion the pain is due to muscle ischæmia and does not occur at the moment of embolism but only after some minutes have elapsed. If the affected limb is actively moved, the onset of pain is accelerated and its severity increased. In support of this view, he quotes several cases in which embolectomy was performed under local anæsthesia, removal of the embolus did not relieve the pain, but as soon as the circulation to the limb was restored, the pain disappeared. Danzís's (1933) experience has been the opposite, he states that pain is relieved as soon as the embolus is removed even although the restoration of the circulation is incomplete. Our experience with cases of aortic embolism tends to support Lewis's hypothesis, the pain was most often referred to the calves and was described as cramp-like. Pain in the abdomen and back can be attributed to ischæmia of the intestines or lumbar muscles as the result of obstruction, either by clot or by spasm, of the mesenteric or lumbar arteries. Whatever the cause of the pain it is difficult to explain why some cases of embolism of the aorta (*e g* Case 12*) or of a peripheral vessel are painless. If the hypothesis that pain is due to muscle ischæmia and is aggravated by movement be accepted, then pain may be minimised or prevented by relative immobility of the ischæmic limb or limbs. This may account for the absence of pain in Cases 12 and 16. In the former, at the time of the embolism, the patient was more seriously ill than any of the other patients and therefore probably did not move her limbs actively. These observations are supported by de Takats (1942) who states that the pain of embolism may be absent in bed-ridden patients.

The most important sign of occlusion of the aortic bifurcation is absence of pulsation in the arteries of both lower limbs, and especially in the femoral arteries. Normally the pulse can easily be felt in the femoral artery just distal to the inguinal ligament and in the external iliac artery just proximal to the ligament. When there is a history of sudden onset of pain and paralysis in both lower limbs, the pulses should always be examined and in these circumstances the absence of femoral pulses should at once suggest the diagnosis of embolism or pseudo-embolism of the aortic bifurcation. It is well recognised that in cases of embolism it is often possible to feel "pulsation" in the artery distal to the site of impaction of the embolus. This apparent pulsation is due to the forward thrust which is exerted upon the occluded artery at each pulse beat (Nordentoft's sign). This thrust is well marked in the aorta (*e g* Case 13), but we doubt whether it could be transmitted to the femoral arteries and there be mistaken for a pulse. However, if the common femoral artery is occluded, it is possible to recognise the thrusting nature of the "pulsation" and sometimes to feel the femoral artery as a firm cord in the femoral triangle (Case 3).

* In Case 16 the onset *may* have been painless. Although the child did not complain of pain, he was very restless and when questioned directly admitted that his feet were "sore". It is well known that children often do not complain of pain in conditions which give rise to severe pain in adults.

The motor and sensory paralysis which is a constant feature in all cases must be attributed to ischæmia, since no other factor is operative. The clinical evidence indicates that paralysis begins at the periphery and spreads centripetally. From the observations on the present cases, it is apparent that there is great variability in the rapidity with which the paralysis develops and in its ultimate extent—compare Case 11, in which within one and a half hours of the onset paralysis extended up to and including the twelfth thoracic segment, with Case 4 in which after forty-eight hours some movement of the thighs was possible and the sensory level was at the junction of the lower and middle thirds of the thighs. Paralysis is observed not only when the abdominal aorta is occluded but also in cases of embolism of the main artery of a limb. In the latter instance, paralysis is due to ischæmia of the peripheral nerves (Lewis, 1936*b*). When the aorta is occluded there is the possibility that ischæmia of the spinal cord or cauda might be an important factor in the causation of the paralysis. The spinal cord is more sensitive to ischæmia than are peripheral nerves, one hour of total ischæmia is sufficient to produce permanent damage (Herter, 1889). Since the spinal cord normally ends at the level of the upper border of the second lumbar vertebra and the aortic bifurcation is usually at the level of the fourth lumbar vertebra, only a very large thrombus would occlude the upper pairs of lumbar arteries* and so interfere with the blood supply to the conus medullaris, but it is possible that the lodgement of an embolus at the aortic bifurcation might cause spasm of these arteries. Even if either of these events were to take place, they could affect the blood supply only to the terminal portion of the spinal cord, and to produce sensory loss as high as the twelfth thoracic segment it is necessary to postulate a vascular disturbance in the cord at the level of the ninth thoracic vertebra. If the spinal cord were damaged, disturbances of micturition should occur, but in none of our cases and in only a minority of those in the literature have these been recorded. Moreover, a successful embolectomy performed as late as nine hours after the initial symptoms has been followed by rapid and almost complete recovery from the paralysis, and therefore it seems improbable that ischæmia of the spinal cord is an important factor in the production of the paralysis. Little is known regarding the susceptibility to ischæmia of the cauda equina and anterior and posterior nerve roots, but it is probable that in this respect they resemble peripheral nerves rather than spinal cord. Santemma (1946) suggests that ischæmia of the cauda equina is the principal cause of the neurological disturbances. He assumes that the blood supply of the cauda equina, like that of the peripheral nerves, is fundamentally regional and that an embolus at the aortic bifurcation which occludes the third and fourth pairs of

* Welch (1910) states that in the majority of cases the last two pairs or only the last lumbar arteries are occluded. In Case 13 in our series at embolectomy it was noted that there was vigorous pulsation in arteries anterior to and on both sides of the lower three lumbar vertebrae.



FIG 36 —Aortic embolism CASE 12 —Posterior aspect of aortic bifurcation six months after embolectomy through the left common iliac artery



FIG 37 —Aortic embolism CASE 12 —To show clot removed at aortic embolectomy (Compare Fig 36)

lumbar arteries, the median sacral artery and its branches the fifth lumbar arteries, and prevents blood from reaching the cauda equina through the lateral sacral branches of the internal iliac arteries, will cause total ischæmia of the intraspinal nerve roots. He further suggests that, if this hypothesis is correct, the level of sensory loss gives an indication of the height to which the embolus extends, for example a sensory level at the second lumbar dermatome indicates that the embolus has occluded the second pair of lumbar arteries. Some of our observations lead us to think that ischæmia of the cauda equina or extraspinal nerve roots may occur in some cases of aortic embolism (Cases 11 and 13), but we believe that it is not the most important cause of the neurological disturbances.

If the common iliac vessels and the fourth and fifth pairs of lumbar arteries are occluded either by clot or by spasm, then the lower limbs and the tissues of the buttock, lower back and lower abdominal wall will be partly deprived of blood. That this happens in many cases of embolism of the aortic bifurcation is suggested by the experience that when the abdominal wall is incised little or no bleeding occurs. The nerves running in these tissues will be ischæmic until such time as the collateral supply from above becomes efficient*. It is not unreasonable to suppose that if this ischæmia lasts for one and a half hours, paralysis might extend as high as the inguinal ligament. In their experiments on centripetal paralysis produced by compression of the arm with a sphygmomanometer cuff, Lewis *et al* (1931) found that after approximately thirty-five minutes the entire limb distal to the cuff was paralysed.

If we accept the view that the initial symptoms do not indicate the moment of lodgement of the embolus but the moment at which the patient becomes aware of the effects of an ischæmia which has already been present for some time, then the time taken for paralysis to extend as high as the groins is even longer. We therefore support the hypothesis that ischæmia of the lumbo-sacral plexus and of the peripheral nerves is the principal cause of the motor and sensory paralyses seen in cases of aortic embolism, and we consider that the rapidity with which the paralyses develop and their ultimate extent are indications of the degree of ischæmia which in turn depends upon the completeness of the obstruction of the bifurcation and the distribution of any reflex vasospasm.

The development of muscle contractures marks the next stage in the evolution of the clinical picture. We believe that the presence of contractures is evidence of a marked degree of muscle ischæmia and that, if they persist for more than a few hours, permanent damage to muscle is inevitable, thus even if complete sensory recovery occurs, the functional result may be impaired by fibrosis of the muscles. In the early stages muscle contracture is reversible, for example, the

* Our clinical observations indicate that some time elapses before contributions from the superior epigastric and lower intercostal arteries are appreciable.

disappearance of the contracture on the left side in Case 10 during spontaneous recovery and the rapid recovery observed in the contractures in Case 11 (right) and Case 12 (left) after embolectomy. If there is hardening of the muscle and contracture of such a degree as to deform the joints, still the condition is not completely irreversible. If the circulation is restored at this stage, the limb may be preserved although the functional result is unlikely to be completely satisfactory. If the ischæmia persists the condition passes into the third stage with soft muscles, lax joints and swelling of the limb. Motor recovery in the affected muscles is no longer possible and amputation may be inevitable. It has not been sufficiently realised that the fate of an ischæmic limb may depend as much upon the state of the muscles as upon the state of the skin. There is an obvious similarity between the stages through which the muscles of a completely ischæmic limb pass and the development of rigor mortis.

Spontaneous recovery from embolism of the abdominal aorta is a rare event. In their series of 193 cases, Albright and Leonard (1950) record 8 patients who recovered the use of the lower limbs without embolectomy. Gesenius (1950) has since reported another case. Data regarding several of these cases are incomplete and it is probable that some of them may have been similar to the 2 cases reported above in which there was "pseudo-embolism" of the aortic bifurcation.

The number of successful cases of aortic embolectomy is now quite considerable. Albright and Leonard (1950) have 26 in their series and their list does not include the cases reported by MacFarlane (1940), Agar (1943), Learmonth (1948, 3 cases*), Keeley (1948), Wilson (1949) and Ewing (1950, 2 cases). Since Albright and Leonard's review, another successful case has been reported by Taylor (1951). A study of the reports of many of these cases shows that, although the operation was successful in that the patient recovered and had good use of the lower limbs, in relatively few of the cases was restoration of circulation and recovery from the neurological manifestations immediate and complete. This corresponds to our experience in the 4 successful cases in the present series.

The explanation for the delay in the return of the circulation after a successful embolectomy is not immediately apparent. It has been attributed to the persistence of arterial spasm (Nystrom, 1936), but this cannot be the whole explanation because the return of the pedal pulses is often delayed for weeks or even months (Table VIII) and indeed they have been reported as remaining absent permanently. This suggests that organic occlusion of the main peripheral vessels has occurred and that when the pulse returns it does so through collateral vessels. Such occlusion could be the result either of the lodgement of portions of embolus which have become separated from the main thrombus at the bifurcation and have been swept on to lodge in peripheral vessels, or of thrombosis occurring in the distal arteries during

* Cases 11, 12 and 14 of the present series

the period of ischæmia. The former is a recognised danger of embolectomy and during the operation steps are taken to occlude the arteries immediately distal to the embolus so as to prevent fragments of the thrombus from being carried onwards. This is likely to happen only when there is a rush of blood past the obstruction and therefore the danger is when the obstruction of the bifurcation is incomplete, it is possible that embolism of the peripheral arteries might occur while an incomplete block is becoming complete as well as during embolectomy. In cases of rheumatic heart disease with auricular fibrillation, another factor which may explain the delay in the return of circulation is the presence of old emboli in the peripheral vessels, the presence or absence of the pedal pulses before the aortic occlusion is seldom known. Case 15 in the present series illustrates two of these possibilities: there were old emboli in the right external iliac and femoral arteries and a recent thrombus at the bifurcation of the left popliteal artery (Fig. 29). Had this patient lived, the return of circulation to the legs could have been through collateral channels only. Although the return of circulation may be delayed, this does not preclude an excellent functional result and, as our observations show, eventually the blood supply to the lower limbs may be more than adequate for all normal needs.

Nor is neurological recovery immediate. We have already considered the development of the motor and sensory paralyses and attributed them to ischæmia of extraspinal nervous pathways. It follows that recovery of function depends upon restoration of blood supply to nerves. It must be stressed that in our successful cases although the longest period before embolectomy was nine hours, this does not represent the longest period for which nerves were ischæmic. Because of the slow return of circulation to the limbs, nerves, particularly those in the distal portions of the limbs, were ischæmic for much longer, probably for as long as forty-eight hours. This is quite long enough to produce organic changes in peripheral nerves.

The general pattern of recovery in the lower limbs is one of steady progression from above downwards, proximal muscles recover before distal muscles and the sensory level recedes distally. Recovery proceeds at the same rate in both lower limbs. In 2 of the cases in the present series (Cases 11 and 13), on one side there was a delay of more than twenty-four hours before function returned in the muscles below the knee. The longest delay was fourteen days. This period is too short to be accounted for by the processes of nerve degeneration and regeneration, and must be due either to a non-degenerative lesion of the nerves of ischæmic origin, or to the effects of ischæmia upon the muscles themselves. The observations upon the small muscles of the feet suggest that in some cases complete denervation and re-innervation of these muscles may have occurred, thus the clinical picture indicates that the degree of ischæmic damage to nerves increases as they pass distally.

Applied to the return of sensation, this hypothesis would lead to

the expectation that if prolonged sensory disturbances were observed they should be of "stocking" or "sock" distribution, and that they should recover by gradual shrinkage towards the periphery. This was precisely the type of sensory disturbance observed in the right leg in Case 14 (Fig 34)

The major sensory disturbances in Cases 11 and 13 were not of this type although in Case 12 at three months a "carpet-slipper" type of sensory disturbance was also present in the right foot. When the residual neurological disturbances in these 2 cases are considered as a whole, we are forced to conclude that in both cases they suggest a root lesion (in Case 11 of lumbar 4 and 5, and in Case 13 of lumbar 3 and 4) rather than a peripheral nerve lesion. The reasons why we consider it improbable that ischæmia of the spinal cord could be responsible for such lesions have already been discussed. The lesions may be due to ischæmia affecting either the cauda equina or the lumbo-sacral plexus. These structures are within the zone of ischæmia created by an occlusion at the aortic bifurcation and we have no means of telling how long they remain ischæmic. Small fragments of an embolus entering one of the lumbar arteries, or the occlusion of the median sacral or lateral sacral arteries might account for serious lesions in these nerves.

There is very little information in the literature of aortic embolism about the reflexes in the lower limbs. Welch (1910) mentions that with complete paralysis the reflexes and electrical excitability are abolished. Rothstein (1935) states that the reflexes vary, they may be diminished, normal or even increased. Our experience has been that the reflexes are invariably diminished or absent. Within as short a period as four hours after the initial symptoms both knee and ankle jerks may be lost. After a successful embolectomy, return of the reflexes was slow and took longer than return of voluntary power in the muscles concerned (Tables XI and XII). When reflexes remained absent, there was always some weakness or loss of tone in the muscles concerned or else there was evidence of persisting nerve lesions. For example, in Case 14 the absent right ankle jerk was associated with weakness of the dorsiflexors and plantar flexors of the foot and with a "stocking" area of sensory loss, and in Cases 11 and 13 the delayed return of the reflexes in the left and right lower limbs respectively was part of the residual neurological disturbances which have been discussed. An absent or equivocal plantar response could be attributed either to weakness of the toe flexors or to diminished sensation on the sole of the foot, often with associated hyperpathia. When the stimulus was applied, the foot was withdrawn but flexion of the great toe was absent. With the recovery of sensation, a normal flexor response was obtained (Cases 11 and 13). On the other hand, ischæmia produces many bizarre effects and it may be that in these cases the explanation for the neurological disturbances is not simple but depends upon scattered lesions through the nerves of the lower limbs.

When embolism at the aortic bifurcation is suspected, heparin

should be given intravenously and if necessary morphine for pain. The trunk and arms of the patient should be heated to about 40° C to encourage vasodilatation. As a result of this treatment improvement in the neurological signs and reappearance of femoral pulses will occur in a proportion of cases in which the precipitating pathological process has been arterial spasm. If improvement is absent after an hour or so, the heparin should be neutralised by an intravenous injection of protamine sulphate, and embolectomy should be performed. We prefer the transperitoneal route, the exact site of the arteriotomy depends upon the appearance of the aorta and common iliac arteries. We do not recommend the administration of heparin in the post-operative period.

SUMMARY

1 The anatomical and pathological features of aortic occlusion are discussed.

2 The clinical features of 11 cases of aortic thrombosis and 16 cases of sudden aortic occlusion are analysed.

We have to thank those of our medical and surgical colleagues who permitted us to see and in some cases to treat certain of these patients.

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TUBERCULOSIS AN INCIDENT OR A DISEASE?

By CHARLES CAMERON, M A , M D , F R C P E , F R F P S G , D P H
Professor of Tuberculosis in the University of Edinburgh

TUBERCULOSIS is not a disease of one tissue or organ, and I wish to discuss certain aspects of tuberculous infection and their influence on the forms which the disease may take and the course it may pursue. These vary with periods of life and to a certain extent with the sexes at these periods. I shall not touch on the vast problem of epidemiology except to remind you that its true appreciation demands the wide view of the trained sanitarian rather than the narrower view of the practising clinician. Too close a focus on the individual may blind one to the more fundamental social and economic origins of the disease.

IMMUNITY—Understanding of the problems of tuberculosis as it affects the individual demands a brief discussion of the pathology of infection and of immunity, for these are not merely problems of site and extent of disease but are bound up with states of immunity and allergy which ultimately determine the fate of the infected person. We know that races exposed to tuberculosis for the first time show little power of resistance, and the classical instance of that was the fate of the Senegalese troops imported into France in the first world war and described so accurately by Borrel (1920). Between their almost complete inability to resist infection and the comparatively high resistance of Western races there is the intermediate state of the American negro race which in its passage through the tuberculosis epidemic is now showing evidence of developing resistance. Western countries, highly industrialised and exposed to centuries of disease, have in the process of time, by the elimination of susceptibles, developed a high degree of immunity, and it is that inborn or natural immunity which forms the first barrier of defence in members of these communities.

Although tuberculosis affects many animals, principally domesticated animals, its course is different from the disease in man, and many animals differ from man in their lack of resistance to the infection, a power which is highly developed in our race. Infection in them pursues an inevitably fatal course characterised by widespread dissemination. Infection in man pursues a similar course in exceptional circumstances only, for natural immunity places a check upon disease and initial infections are overcome by the majority. In the minority the infection becomes firmly established and passes to disease which in some cases, which are exceptional in races of high resistance, leads to dissemination similar to that so often seen in animals.

A Honyman Gillespie Lecture delivered on 11th October 1951

THE PRIMARY INFECTION —The first infection, whether it is held in check or advances, follows a characteristic pattern, that of the primary infection. The pattern of this infection is well known—the small focus at the point of tissue entry, usually the lung substance, which tends to caseate rapidly and to heal, the rapid passage of the organism into the lymphatics and the swelling of the draining lymph glands. It is this combination of primary focus and glands which constitutes the primary or Ranke complex. The primary focus in the lung field is the so-called Ghon focus. Primary complexes may form in fauces and neck glands, in intestine and mesenteric glands, in skin and regional glands. In all, the glandular is usually, from the disease point of view, the presenting and predominating element.

With extensive involvement of the lymphatic glands, particularly when the complex is in the lungs and the glands involved are mediastinal, intermittent passage into the blood stream of lymph cells carrying tubercle bacilli takes place and in this way, coincidently with the development of the complex, there is seeding of tubercles in other tissues and structures. This is something quite different from the sudden eruption of a caseous focus which leads to acute miliary dissemination. It is a silent process which may never declare itself, or may only do so months or even years later by a progressive focus in bone or joint, or genito-urinary tract, or lymph glands, or serous membranes. During this phase sparse tubercle seeding of the lungs may also take place with apparent regression and even hyalinisation, and it is these seedings which are believed to play a part in the later development of ulcerative lung tuberculosis. This period of primary and post-primary dissemination is the key to our understanding of many of the later phenomena of tuberculosis.

The pattern of the primary infection is determined by the absence of tissue sensitivity. That, as you know, develops about six or eight weeks after the infection—earlier if the infection has been heavy or repeated, later if the infection has been light. With it comes that altered reactivity of the body to which v. Pirquet gave the name of allergy, and then the body reactions change completely. Tuberculous lesions developing after this period do so in tissues which react violently to the infection, and the characteristic of these lesions is the rapid tissue caseation and destruction. There has been much controversy on the relationship of allergy to immunity and I do not propose in this talk to enter that controversial field. There is little doubt that they are separate entities. Immunological studies suggest that innate and acquired immunity rest on similar cellular foundations, and the ability of innate immunity to localise and heal the primary infection before allergy has developed is well known. The rapid caseation and destruction of later lesions is the result of the allergic state of the tissues and it is easy to assume that the action of allergy is wholly deleterious, but the localising effect of allergy in subsequent infection and its destructive effect on the immobilised bacilli should be borne in mind.

It develops along with acquired immunity and it may have potentialities for harm or for good. It is certain that the two go together, and high degrees of immunity often, in clinical practice, go with high degrees of allergy.

STAGES OF THE TUBERCULOUS INFECTION—In referring briefly to what is often termed Ranke's theory or Ranke's hypothesis, I do so not because it is accepted nowadays but because Ranke recognised certain stages of tuberculous disease and attempted to co-relate them with certain degrees of allergy. His first stage covered the period of development of the primary complex and terminated with the appearance of allergy. The second stage was said to be characterised by extreme degrees of tissue sensitivity, and Ranke related this to dissemination of the infection by lymph, blood, and tissue channels. With a postulated waning of hypersensitivity the third stage of isolated phthisis was reached. It is impossible to fit all tuberculosis into these convenient compartments and one certainly cannot relate the different disease phenomena so accurately to different degrees of allergy, but the theory is of service in calling attention to three definite periods of infection which, despite acknowledged variations, form a framework on which to build an understanding of the tuberculous process.

It is not my intention to discuss in detail the primary infections. The majority of these are silent. They give rise to no symptoms and they are dealt with effectively by the forces of inborn immunity. They produce no clinical signs and may show no radiographical evidence of their presence. The conversion of the tuberculin reaction is the only proof that infection has taken place, but, however small the lesion may be it is believed that conversion will not take place unless tuberculous tissue has formed. Many children live in contact with infectious adults and remain tuberculin-negative, and it is probable that their inborn immunity is sufficient to deal immediately with the tuberculous infection and prevent it from being implanted in the tissues. Although we use the skin as an index of tissue sensitisation there is evidence that the skin is not always representative of body sensitisation. Furthermore, allergy to tuberculous infection is not always elicited by tuberculin and it may require the employment of the whole bacillus (B C G) for its detection. Even when the primary infection gives rise to gross lesions there is a high recovery rate and many lung complications of the glandular component resolve completely.

When we talk of a dissemination phase of the primary infection we must remember that this may be of short or long duration, that the disseminations may be abortive, may declare themselves shortly after their implantation, or may do so only after a long interval. Furthermore, there may be secondary disseminations from those sown at an earlier date. Even with these limitations the conception of this phase is useful, for it is during it that the seeds of disease in tissues other

than the lungs are sown. There is also evidence that deposits sown in the lungs at this time may be responsible for later ulcerative disease of these organs.

These extrapulmonary lesions form an interesting group, for, in the majority of cases, they are not associated with lung tuberculosis, and on the other hand lung tuberculosis in the majority of cases is clinically an isolated phenomenon and is not associated with disease of tissues which infection cannot reach by the tubular pathways. It is, of course, by these pathways that the common complications of larynx and intestine arise.

ALLERGIC PHENOMENA —It is in the early stages of the evolution of the primary infection that certain disease states commonly attributed to the allergy of the tissues arise, and the commonest of these are tuberculous rheumatism, certain conditions of the skin, principally erythema nodosum, and of the eye, principally phlyctenular conjunctivitis.

Tuberculous Rheumatism —Tuberculous rheumatism has a long history and there is evidence that certain cases of chronic polyarthritis are of tuberculous origin, but that is not the type which is encountered in the early stages of the tuberculous infection. Those who have taken many histories of tuberculous patients must have been struck, as I have been, with the frequency with which a previous history of rheumatic fever is given. Yet these patients show no evidence of cardiac damage and the description of painful joints is not that of the inflamed intensely painful joints of acute rheumatism. Sometimes the rheumatism appears to be in muscle or fibrous tissue but usually it is stated to have involved several joints, to have disappeared without treatment, and to have left no residual disability. While similar attacks may occur during the course of an established tuberculous condition they occur usually before the tuberculosis has proclaimed itself and there seems to be little doubt that the condition is an allergic phenomenon. A similar arthritis often accompanies erythema nodosum which is accepted as having a similar ætiology and attacks of erythema nodosum may also occur during the course of established disease.

Erythema Nodosum —The tuberculides are skin eruptions which are associated with tuberculosis of some other part of the body and they are now considered to be analogous to syphilides, trichophytides, etc., and to be caused by emboli of tubercle bacilli in the sensitised skin. Erythema nodosum is not a true tuberculide and the tuberculides in fact do not occur during this early phase of the infection. Although a majority of cases of erythema nodosum in this country is due to tuberculosis, an appreciable percentage is due to other causes, and the disease is best regarded as a syndrome caused by different allergens, bacterial or toxic. The few recorded cases of finding of tubercle bacilli in the lesions are not fully authenticated. When the syndrome is of tuberculous origin it almost always appears with the development of allergy, and this fact enables us to fix the primary infection at some

period within the previous six to twelve weeks. Instances of erythema nodosum of tuberculous origin recurring several times during the course of tuberculous disease, as I have already stated, are not uncommon.

Phlyctenular kerato-conjunctivitis—Phlyctenular kerato-conjunctivitis also often makes its appearance during this period and it is considered to be an allergic phenomenon due, in the majority of cases, to tuberculous infection, but in a minority to other causes. It differs from tuberculous rheumatism and erythema nodosum in running a more protracted course, for the phlyctenular masses ulcerate readily and infected ulcerative lesions often result. It is mainly a disease of childhood and in many children the attacks recur. There is obviously an underlying systemic cause and it is interesting that it manifests itself in this peculiar sensitivity of the superficial eye tissues. Like erythema nodosum the lesion is met with more frequently in certain age groups. The former occurs around, and in the early years of, puberty. The latter occurs in childhood, and both appear to be commoner in Scandinavian lands. Erythema nodosum has a much heavier incidence in females than in males. It is not at all clear why these two tissues are involved so frequently in these phenomena. It is known that some poisons, *e g* lead, involve certain tissues, and certain organisms and viruses have a similar tissue electivity. Erythema nodosum and phlyctenular kerato-conjunctivitis develop during the primary tuberculous infection, the main element of which lies in glandular tissue, and it is believed by some (Brun and Viallier, 1948) that it is a specific product of the growth of tubercle bacilli in gland tissue which has this special affinity for skin and eye. I shall come back to this theory later.

POST-PRIMARY DISEASE—With the passage of this phase which is of uncertain duration and may never be detectable as a phase at all, the so-called post-primary phase is entered. This phase by definition covers all tuberculosis which is not definitely a primary infection phenomenon and it may be said to cover the future life span of the tuberculous individual. Many tuberculous lesions develop in the years which immediately follow the primary infection and it is useful to designate these as the early post-primary infection years. In the earliest stages of this period, often in the first three months, appear *tuberculous meningitis* and *acute miliary disease* of young children, and within the first two years, very often within the first year, there appear the metastatic *bone and joint lesions* which are a common feature of the mid-childhood years and of adolescence. These lesions are quite often multiple as one would expect in blood-borne conditions, and they may involve many tissues other than bones and joints. Why some tissues like muscle escape completely—I have only once seen tuberculosis of skeletal muscle—and why others like thyroid are seldom affected is an interesting problem. Even when only one bone or joint or viscus is involved clinically, disseminations into other areas

have usually taken place, and the *bone marrow* is often invaded at a quite early stage of the dissemination period. The involvement of this tissue in typhoid is well known, and sternal marrow puncture for purposes of culture (Hirsowitz and Cassel, 1951) has been employed. The use of this procedure in the diagnosis of disseminating tuberculosis yields positive results in an appreciable percentage of cases (Schleicher, 1946, Horowitz and Gorelick, 1951) and is a useful diagnostic adjunct when diagnosis is in doubt.

Pleurisy—Pleurisy with or without effusion appears in a preponderance of cases during the first year after the receipt of the primary infection. Its exact pathogenesis is in dispute but its time of appearance and its significance should be recognised. There are many points about this condition which are of great interest. It is not often seen in childhood and the majority of cases occur between the ages of 15 and 25. There is no explanation of its rarity in childhood any more than there is of the rarity of ulcerative pulmonary tuberculosis in these years, and this is all the more interesting when one considers the fact of its intimate relation to the primary infection. This fact links it with primary infection acquired in adolescence, but there is no agreement on the actual pathogenesis of the condition. While some cases of tuberculous pleural effusion start insidiously, many have an abrupt onset with fever, pain in the side, and pneumonia-like symptoms, and one cannot escape the conclusion that the suddenness of the symptoms indicates an allergic reaction. As by careful cultural examination tubercle bacilli can be found in a large percentage of the exudates, direct infection of the pleura by eruption of a caseous subpleural focus or of a caseous glandular focus seems likely. Of greater interest is the future tuberculosis morbidity which is undoubtedly high, varying as it does in different series from 20 per cent to 40 per cent, and influenced probably by the care given to treatment at the time. The most frequent subsequent lesion is tuberculosis of the lungs and this develops often within a year, and very often within two years, of the effusion. The lung lesion may be of the typical so-called reinfection subclavicular type which leads to bronchogenic tuberculosis, or it may be of the bilateral apical type which leads so often to sluggish lung tuberculosis which remains so long confined to the upper lobes. This type is probably of blood-borne origin. The origin of the subclavicular infiltration is disputed, and it is worth remembering that when it develops it is not always on the side of the pleurisy. Some effusions are followed by tuberculous lesions of bones, joints, kidneys, or other extra-pulmonary tissues, and there is general agreement that pleurisy is an early manifestation of tuberculous infection which may terminate in pulmonary or extra-pulmonary disease.

Tuberculosis of extra-pulmonary tissues is common in childhood during the years when ulcerative tuberculosis of the lungs is rare, but it is also common in the early years of adult life when this type of lung tuberculosis is frequently encountered and is, in fact, responsible

for a very high mortality. While it is true that extra-pulmonary tuberculous lesions are not commonly associated with progressive lung tuberculosis and while the converse is also generally true, the facts hold good in a clinical rather than in an anatomical sense. Nevertheless, from the behaviour of the tissues involved the two types of disease are different clinical entities. For all that, pulmonary tuberculous lesions are fairly common accompaniments of extra-pulmonary tuberculosis (Mann, 1946, Hawkins and Thomas, 1946, Marienfeld, 1938, Pagel, 1938) but in children the pulmonary disease is practically always the primary lesion from which the hæmatogenous spread occurred, and in adults it is of a type which suggests a blood-borne origin and clinically shows a greater tendency to healing than does ulcerative bronchogenic tuberculosis. The latter does, however, occur. Pleurisy can thus be a precursor of blood-borne disease of extra-pulmonary tissues or of two clinically different types of lung tuberculosis. Even if the pathogenesis of the re-infection type, subclavicular in site, is unknown, we must grant that it too may be a hæmatogenous lesion. In support of this is the fact that while the majority of lung lesions which accompany blood-borne extra-pulmonary tuberculosis are bilateral and of similar origin as judged by their distribution and radiographical appearances, an appreciable number conform to the re-infection type of lesion and behave as such (Marienfeld, 1938, Pagel, 1938). Post-primary tuberculosis can thus be of two distinct types which are partly determined by age, but they show a considerable degree of overlapping as some of the lung lesions which accompany bone and joint or other blood-borne diseases are of the bronchogenic type even when they are later developments. Furthermore, in a fairly high percentage of cases of chronic lung tuberculosis blood-borne lesions of other tissues develop. They may not present clinical symptoms during life but they are easily detected post-mortem (Willis and Rosenthal, 1945).

Chronic Disseminated Tuberculosis—There is a type of tuberculosis, usually met with in young adults, lasting often for a large number of years, and characterised by the development of successive lesions in various extra-pulmonary tissues. Many of these cases start with pleurisy and the lesions may involve joints, bones, serous membranes, glands, soft tissues, skin, and genito-urinary tract. Very often the lungs also are involved in a hæmatogenous type of disease. Each lesion leads as a rule to rapid initial destruction of tissue and when healing appears to be in progress it is followed by a new lesion in some other site. The disease lasts over many years and cure is possible. It is for this type of disease that the term "chronic disseminated tuberculosis" suggested by Pagel should be reserved. The lesions in this type of disease probably come from a central lymphatic focus and the disease is characterised by high tissue sensitivity. The healing of the lesions suggests the building up of local tissue immunity and the repetition of the disseminations suggests

a low state of general immunity. This conception of local tissue immunity explains many puzzling clinical manifestations of tuberculosis. In chronic ulcerative pulmonary tuberculosis, as I have already stated, disseminations are common, but clinical disease in other tissues or organs is rare, and it may be that the type which post-primary tuberculosis will take is determined in the first instance by the general and local tissue immunity of the individual. In adult life the common pattern of disease is isolated tuberculosis of the lungs.

Genito-urinary Tuberculosis—Tuberculosis of the genito-urinary tract is a blood-borne manifestation and it may involve the components of the tract singly or in combination. It is a not infrequent complication of chronic pulmonary tuberculosis, the kidney being involved in about 8 per cent of all fatal cases and the genital tract in about 10 per cent of fatal cases in men and 5 per cent in women. The incidence in non-fatal lung disease is certainly less. Renal involvement is very common in the chronic disseminated type of tuberculosis which I have discussed, but it is often a silent condition and is detected comparatively late in the disease. When it occurs as a solitary clinical tuberculous manifestation it appears in relation to the primary tuberculous infection at a much later date than bone and joint tuberculosis. This fact has been discussed by Ustvedt (1947) and Ustvedt and Wergeland (1949) who point out that an interval of more than ten years separated the two conditions in a large percentage of a series of cases which they were able to follow from the time of the primary infection. There is little doubt that the kidney infection is sown during the early dissemination phase and that the development of the disease to a stage when symptoms are produced is relatively slow. The frequency of kidney involvement in patients suffering from non-pulmonary tuberculosis was pointed out by Medlar (1926) and is well known clinically to those who have been interested in this type of disease. Band and Munro, quoted by Munro (1944), found an incidence of tubercle bacilluria in 21.6 per cent of 300 cases of pulmonary tuberculosis, and in serial sections of 33 pairs of kidneys from these patients found giant cell systems in the cortex in every instance. Munro (1944) found a similar incidence of kidney involvement in children passing through a primary tuberculous infection and recorded the presence of tubercle bacilluria in 19 per cent of 188 such children, a minority of whom had grave tuberculous lesions. Only four died and he was able to secure three pairs of kidneys. None showed any naked eye evidence of tuberculosis but in all serial sections showed bilateral tuberculous lesions, usually more advanced in one kidney. These positive findings are very much higher than the incidence of clinical renal tuberculosis and demonstrate the frequency of renal involvement and also the frequency of its healing. The clinical incidence of renal tuberculosis in patients suffering from pulmonary tuberculosis does not exceed 5 per cent.

Tuberculosis of the Skin—I have referred already to the question

of local tissue immunity and to the greater resistance of certain tissues to tuberculous infection. The tuberculosis physician, and by that I mean the physician who handles all types of tuberculosis, sees little of tuberculosis of the skin. That is partly because skin lesions are referred to the dermatologist, but apart from that the development of tuberculous skin lesions in patients under his daily care is not frequent. With the exception of the *scrofuloderma* group in which the skin is infected from underlying tuberculous disease or adjacent mucous membrane tuberculosis, and of the rare cases of direct infection of the skin, all skin lesions are of blood borne type. The commonest is *lupus vulgaris* and this may involve multiple areas of the face, trunk, and limbs, although it occurs with greatest frequency on the face and in the nose. This group represents true tuberculosis of the skin. Scrofuloderma and lupus arising from underlying lymph gland tuberculosis, are of course, of local origin, but much lupus is of hæmatogenous origin. The *tuberculides*, unlike true skin tuberculosis, are evanescent phenomena. Although tubercle bacilli have been found in the lesions of all of the group—*lichen scrofulosorum*, *papulo-necrotic tuberculides*, and *erythema induratum*—they are regarded as eruptions produced by the action of emboli of tubercle bacilli on allergic skin. They usually occur in young adults or children and while there may be a history of tuberculosis or concomitant tuberculosis of bones, joints, glands, etc., very often the patient comes, or is brought, for advice on account of the skin eruption. Although the tuberculides are obviously blood borne deposits they are not common. They may appear at any time in the course of the disease or after the date of infection and, apart from erythema induratum and papulo-necrotic tuberculides of the extremities in which circulatory stasis may be a predisposing cause, it is usually impossible to say what determines their appearance. They are practically never seen in patients who are ill from tuberculosis and they are associated with mild types of tuberculosis and a good general condition. It is interesting that lupus is very often an isolated phenomenon, and if there is associated tuberculous disease it is, as a rule, benign. It is established (Rich, 1944) that tubercle bacilli can become attenuated in the skin, but this does not altogether explain the comparative rarity of tuberculides and tuberculosis of the skin, or the infrequency of their association with other forms of active tuberculosis.

Tuberculosis of Lymph Glands—If we exclude the disseminated tuberculosis of lymph glands which is a common feature of progressive tuberculosis of primitive races and is rarely seen in races with greater inborn resistance to tuberculosis, lymph gland tuberculosis in this country is usually the glandular component of a primary complex. It has been my experience that children who recover from extensive glandular tuberculosis, whether of cervical, mediastinal, or abdominal origin, very rarely develop further manifestations of tuberculosis at a later period. Clinical experience should not be the foundation of

dogma, but the experience of the Frenchman Marfan that those who had suffered from tuberculous cervical adenitis which had healed before adolescence rarely developed pulmonary tuberculosis, has become exalted to a law which is still spoken of as *Marfan's law*. Nothing is absolute in Medicine, but clinically this observation holds true. In the skin we have a tissue which seems to have a high natural resistance to tuberculosis but which paradoxically seems to be involved when general resistance to tuberculosis is high. The lymph glands bear the brunt of primary tuberculous infection in childhood, and recovery seems to lead to a high degree of acquired resistance (Wilkinson and Curetin, 1943) against subsequent tuberculous disease.

The ability of tubercle bacilli to survive for long periods in lymph gland tissue is well known, and in fact one of the theories of the much disputed origin of pulmonary tuberculosis is founded on this fact. These theories ignore the anomaly of organisms living an apparently saprophytic existence in one tissue and producing disease in another, but if we grant the possibility of varying degrees of local tissue immunity there need be no difficulty in accepting them. No one with any real knowledge of tuberculosis believes that the state of allergy of any one tissue is representative of that of the body as a whole, but it is a new conception that the action of the growth of tubercle bacilli on different tissues may produce different allergens which have a selective action on different tissue systems of the body.

Tuberculosis of the Abdomen —It is doubtful whether one is justified in including in this condition the ulcerative lesions of the bowel which complicate a large percentage of cases of pulmonary tuberculosis. The commonest abdominal tuberculous lesions are of primary origin, basically glandular in type, with varying degrees and types of peritoneal involvement and many of them are due to bovine infection. The peritoneum may be involved in the multiple serosal involvement which occurs as a post-primary blood borne phenomenon and it is often picked out by acute miliary tuberculous disease. The localised hyperplastic forms which involve principally the terminal ileum and cæcum, and occasionally the distal colon, form an interesting group. They are rarely associated with other obvious tuberculous lesions and they conform pathologically to a primary type of infection.

Tuberculosis of the Eye —Tuberculous lesions of the eye have always presented a difficult problem. Some are of bacillary origin and their pathogenesis and pathology are not in dispute. Others—and these include the vast majority of cases (Duke-Elder, 1939)—whether it be keratitis, scleritis, iritis, choroiditis, retinitis, etc., present a non-descript non-specific clinical and pathological picture and their relation to tuberculosis may be deductive or even inferential. These lesions may be equally attributable to non-tuberculous disease in different areas of the body, but they are often associated with occult tuberculosis, usually of lymph glands. It is difficult to understand why the tissues of the eye should be affected by distant tuberculous

foci which appear to be innocuous to the rest of the body and it is believed (Duke-Elder, 1939) that the essential factor in these common inflammations is a hyper-sensitive or allergic state of the ocular tissues themselves. I have already stated that the sensitivity of the skin is not a true index of the sensitivity of other tissues. It is well known to those who have experience of tuberculosis in its many manifestations that certain types of tuberculosis, particularly tuberculosis of peripheral glands which have undergone caseation, give rise to very high degrees of skin sensitivity, and some tissues, for reasons which we do not understand, may acquire greater sensitivity than others. There is very often a family tendency to particular manifestations such as those in skin and eye, and repeated exposure of these tissues to the allergens increases their sensitivity. "It is thus" states Brun (1949), "that successive reinfections in one segment of the eye end by creating a state of local susceptibility, latent and chronic, a veritable fire which smoulders under the embers of a focus which is never extinguished and which anything may fan into flame."

Tuberculous eye lesions are not common and are seldom seen with active pulmonary tuberculosis, but they are not infrequently associated with healed tuberculosis of the lungs or with infection of the lymphatic glands, particularly those of the lung roots (Duke-Elder, 1940). This author concludes that, with the exception of acute miliary tuberculosis, tuberculosis of the eye "occurs with the greatest rarity in the presence of active tuberculosis elsewhere but rather in apparently normal healthy well-nourished individuals with a healed or benign tuberculous infection in some organ, usually the lymphatic system in the chest, more rarely in the lungs, the glandular depot, even although it is usually slight, quiescent, clinically healed or calcified, being capable of disseminating infection after the primary pulmonary focus has healed, presumably by the occurrence of an intermittent bacillæmia which is usually without systemic significance." Brun (1949) makes an almost similar statement and emphasises that when tuberculosis of the eye does develop with lung tuberculosis it is usually after the lung disease has healed. He states that these lesions are practically always associated with foci of tuberculosis in glands and that the eye manifestations are a late development of infection. The gland foci themselves are often old and latent and the same is true of visceral foci when these are present. He claims that the allergens are a specific product of the growth of tubercle bacilli in gland tissue and that they have an elective action on mesenchymal tissue. Eye tuberculous lesions are to him a mark of immunity against progressive lung tuberculosis. The two conditions develop in entirely different soils, and it is there that we see the explanation of the apparent antagonism which exists between lesions of skin, glands, and eye on the one hand and lung tuberculosis on the other. The latter disease is also entirely different from the chronic disseminated tuberculosis which I have discussed. Perhaps at the other extreme

where anergy is the rule lies sarcoidosis, and it is interesting that the soil which favours these particular non-pulmonary tuberculous states can be influenced by diet (Cameron, 1951) and very often by calciferol. Both appear to affect the background of the disease and in this way modify its course.

Chronic Pulmonary Tuberculosis.—The principal tuberculous lesion, the one which constitutes our main social and therapeutic problem, is tuberculosis of the lungs. No satisfactory explanation has been given of why this condition is so rare in childhood and why it appears so suddenly and with such frequency in young adult life to become, as it were, the pattern of adult tuberculosis. It is to a very large extent a one organ disease and we can understand the involvement of that organ when we reflect that the majority of tuberculous infections are acquired by inhalation and that the lung capillaries constitute a filter for all venous blood and are likely to arrest tubercle bacilli which have entered the circulation from lesions elsewhere. The cavity formation characteristic of allergic tissue, and the spread by the air passages to other areas of the affected organ or its neighbour, are also understandable. It is not a disease which as a rule is associated with high cutaneous allergy and, except in its terminal phases, it is not marked by blood dissemination although these disseminations do take place. They rarely, however, progress to disease, and tissue resistance including that of the lung itself is obviously high. It is this resistance which makes it amenable to surgical methods of treatment which overcome mechanical obstacles to healing and it is this resistance which, reinforced by good conditions of hygiene and diet, by itself can finally effect cure. I have already discussed the apparent antagonism between chronic lung tuberculosis and other types and forms of tuberculosis and I have stated that there are differences in the human soil in which these various types flourish. If we say that they thrive in varying humoral states we are no more specific, but it is an interesting fact that they are types each of which seems to follow a definite course. We do not know why lung tuberculosis appears so suddenly at puberty or why it tails off at the end of the sexual life of the female and is prolonged into, and even intensified in, a later period of male life. The procreative life of the male covers a wider span than that of the female and this type of lung disease does seem to be associated with that period of life. It is extremely sensitive to social, economic, and nutritional factors, but it remains the type of tuberculosis of adult life.

There is growing evidence that pulmonary tuberculosis is in many cases intimately related to the primary infection, particularly when that infection is acquired in early adult life, and then it appears often within two years and very often within five of its establishment. Other cases develop at periods which are more remote from the infection. In the one we see the efflorescence of the seed. In the other we suspect that a new sowing has taken place. So we have the *chrysois* and

exogenous theories, both of which are true. The localisation of the disease to the upper areas of the lungs is probably dependent on the dynamics of the pulmonary circulation (Dock, 1946, 1947) and is not a point which I shall discuss here. Neither shall I discuss the problems of tuberculous meningitis which formed the subject of a recent lecture.

I have tried in this talk to fit into a clinical picture the ramifications of tuberculosis in the human body, to present them as parts of one pathological process, and to integrate them with varying degrees of resistance of the tissues of the individual. What I have discussed are essentially clinical problems, but tuberculosis has wider issues. While it is possible to draw a fairly composite picture of the disease, many things remain which we do not understand. The title has asked a question—is it incident or disease, the incident in the individual or the repercussions on the community? A narrow outlook and a restricted interest in Medicine may focus interest on solitary incidents in the individual to the exclusion of the disease itself. A wide outlook on the problems of disease and a catholic interest in Medicine take us into problems of greater issue to the individual and the community. Tuberculosis is fundamentally an incident in the individual and a disease in the community. It has many facets and it is not capable of solution by slogans or formulæ. It admits of no solitary answer, for behind it those with understanding see social and economic issues which must be faced before the disease and its incidents can be eliminated. The soil of the individual influences the incident. The soil of the community influences the disease, and it is there that our greatest problem lies.

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OBITUARY

DR ROBERT DURWARD CLARKSON

By the death of Dr Robert Durward Clarkson, former superintendent of the Royal National Institution for the Mentally Defective at Larbert, on 6th November 1951, Scotland lost a distinguished Physician and Psychiatrist, and one of the foremost authorities on Mental Deficiency

A scholarly man and one of outstanding ability, he had a distinguished career at Edinburgh University graduating B Sc in 1866 at the age of nineteen and M B, C M four years later. In 1906 he obtained the degree of Doctor of Medicine, his thesis for that degree being on "Mental Deficiency," and in 1910 his Fellowship of the Royal College of Physicians of Edinburgh. After graduating he occupied various hospital posts, including the Edinburgh Royal Infirmary and the Sick Children's Hospital, where he was closely associated with the late Dr John Thomson, working with him in his clinic for mentally defective infants and young children. He then took up general practice in Falkirk where he was in very truth "The Beloved Physician" and was appointed visiting medical officer to the Royal Scottish National Institution in 1895. In 1911 he became resident medical superintendent, a post he occupied till he retired in 1935.

His thoughts and interests were early turned to mental deficiency when, as a boy, holidaying in the country he found the defective son of a farmer tied up in a byre for his own safety. His talks with the boy and the sympathy aroused made a deep impression on him, an impression which remained with him all his life. Dr Clarkson's knowledge of mental deficiency and his understanding of the defective were in advance of his times. At the time he entered the Institution, little was known about Mental Deficiency. The Royal Commission had not issued its report. There were no Mental Deficiency Acts. At that time the general public took the view that nothing could be done for defectives and that permanent custodial care was necessary for their own safety and that of the community. Dr Clarkson at once took up the cudgels on their behalf, declaring emphatically that the well educated, trained and understood mental defective could become socially efficient and an asset rather than a liability.

At that time, too, the I Q was unknown, yet Dr Clarkson could diagnose and assess with a skill and accuracy unsurpassed to-day.

He spoke on many platforms and expressed his opinions with a forcefulness and earnestness which carried conviction. He proceeded to put his views into practice and very soon had an excellent Special School established within the Institution and also developed training facilities for older patients. His great desire was to have a separate colony for adults, and this was achieved in 1934. The colony, situated in beautiful surroundings, now stands, a worthy memorial to his foresight and vision.

Dr Clarkson was one of the founder members of the Scottish Association for Mental Health. There his advice and help were invaluable and were eagerly sought and freely given, not only in matters pertaining to mental deficiency, but also in the wider field of mental health. A man of deep religious convictions, he stressed the great importance of religion in the field of mental

health and of bringing the churches into it. On a number of occasions he gave evidence on behalf of the Association to Governmental Committees, notably the Committee on Protection and Training, the Russell Committee and the Committee on the Scottish Health Services. He also represented the Association at the Second International Congress on Mental Health in Paris in 1936.

He went to live in Perthshire on retirement, but remained consultant to the Institution and the Stirling Infirmary, served on various Medical Boards and continued to take an active interest in the work of the Voluntary Association. During the war years he and his family kept open house for serving men and women from overseas. Two hundred and thirty-eight took advantage of this, some returning on every leave. They came from Canada, New Zealand, Australia, South Africa, France, Belgium, Holland, Norway, Poland, U S A and two from the Argentine, and many grateful letters from the boys and girls so far from home showed how much this was appreciated.

Throughout his life he kept an open mind, always ready to listen and pay attention to the views of others. A man of great charm and ability, he was of a retiring disposition and simple tastes who sought neither publicity nor position, but merely to serve others. By his love, sympathy and understanding he brought happiness and a new hope to the lives of so many. This was very evident by the number of his old patients who later visited him, some to seek further advice and guidance, and all to thank him.

As one of his children said of him—"His was the humility of the truly great. He gave us, his children, eyes to see with, which we could never hope to use with his patience and perception. But what a legacy! What a trust!"

Those of us who had the privilege of knowing him and of working with him feel that he has left to us also a great trust.

NEW BOOKS

Electroencephalography in Clinical Practice By R S SCHWAB, M D Pp 195, with 106 illustrations London W B Saunders 1951 Price 32s 6d

This book is addressed to "neurologists, internists, psychiatrists and neurosurgeons" rather than to electroencephalographers. It is surprising, therefore, to find that only three of the nine chapters deal specifically with use of the E E G in disease and that whilst there are eleven half-tone blocks illustrating different types of electrode and electrode holders, epilepsy is dismissed in 23 pages. One of the figures (p 92, Fig 63) is said to be the electro-encephalogram of a case of "severe epilepsy" with "clinical evidence of deterioration" but the record corresponds closely to the pattern seen in subacute progressive encephalitis. Surface electrodes were first used by Adrian and not by Gibbs as the author states. The text appears to have been hurriedly written, a phrase such as "drawing his attention olfactorily to the smell" should have been recast. The book is well produced and it is useful to have Dr Schwab's numerous contributions to electroencephalography summarised.

Management of Celiac Disease By SIDNEY V HAAS, M D, and MERRILL P HAAS, M D Pp 188, 15 illustrations London Lippencott 1951 Price 40s net

This is an excellent book, most of its pages being devoted to a review of literature. There are 668 references. The etiology of the condition, which is frequently familial, is quite unknown, but the authors think that there is some mechanism in the intestinal tract whereby polysaccharides are converted into substances that irritate this tract. Diagnosis may be difficult, and perhaps fibrosis of the pancreas is not a separate condition but due to severe celiac disease. Treatment should be chiefly dietetic and the authors claim excellent results in 370 cases treated with a diet consisting at first of banana, protein milk, meat and cheese as a basis. Under such a regime recovery should be complete with no relapses, no deaths, no crises and no stunting of growth.

Chronic Bronchitis By TREVOR HOWELL, M R C P ED Pp viii+111, with 3 plates London Butterworth & Co (Publishers) Ltd 1951 Price 17s 6d

This is an essentially practical book by an author with much experience of the problems of chronic bronchitis in geriatric practice. The ætiology, pathology and symptomatology are fully discussed before going on to the actual management of the patient. Full details are given of controlled experiments with expectorant drugs, and their usefulness is questioned. Greater success may be expected from the proper employment of antispasmodics and antibiotics with a place for physiotherapy. It is emphasised that each case must be looked upon as a separate problem. This easily read book may be thoroughly recommended.

Dianetics By L R HUBBARD Pp xvii+413 London Derricke Ridgway 1951 Price 30s net

This shamelessly pretentious book, subtitled "The Modern Science of Mental Health," is a contribution not to science but to mumbo-jumbo. Orthodox psychiatry is abused and in its place is introduced "The Hubbard Dianetic Foundation Inc," with the discoveries of "the single source of mental derangement," and "a therapeutic technique with which can be treated all inorganic mental ills and all organic psychosomatic ills, with assurance of complete cure in unselected cases." What is new in Dianetics is mostly nonsense, and rather dangerous nonsense. An extraordinary transatlantic mixture of sophistication and ingenuousness, it is of interest only as a pathological cultural symptom.

Clinical Unipolar Electrocardiography By B S LIPMAN and E MASSIE Pp 232
with 191 illustrations Chicago The Year Book Publishers 1951 Price \$5

In 135 pages of text this book gives a straightforward explanation of the unipolar lead patterns commonly encountered in clinical practice The arrhythmias are not considered The principles of electrocardiographic interpretation are based on the pioneer work of both Wilson and Goldberger, explanations are clear and balanced

The liability to error in basing a diagnosis of ventricular hypertrophy on the voltage of the QRS complexes alone, the importance of serial electrocardiograms in diagnosing obscure myocardial infarction, indications for additional leads, the changes associated with potassium and calcium serum levels are all carefully explained

There are 63 pages of illustrative electrocardiograms at the end of the book They suffer from the faults of the direct-writing electrocardiograph employed, but are reasonably clear The legends are the least satisfactory part of the book, hypertrophy is repeatedly referred to as enlargement and the explanations are not always clear or satisfactory

At \$5 this useful little book is expensive for the British reader

Diabetes Control By EDWARD L BORTZ, M D London Henry Kimpton 1951
Price 25s

This book is written as a guide for the diabetic patient Every aspect of diabetes is considered including early detection, causal factors, psychology of the diabetic, life insurance and dietetic and insulin treatment The rules which the diabetic must follow are discussed in detail, with perhaps rather too much repetition

The explanation of diet planning seems unnecessarily involved There are thirty pages devoted to meal planning The recipes and foods suggested are, of course, American and in many cases are not available in this country

While there is much of value in this book, the average patient might find it rather beyond his requirements

The Genetics of Micro organisms By D G CATCHESIDE Pp 223, with 49 tables
and 35 figures London Sir Isaac Pitman & Sons 1951 Price 21s net

Since Pasteur's use of a micro organism in the preparation of isomers, Leeuwenhoek's "anamicules" have become increasingly popular as a convenient form of guinea pig The basic sciences owe much recent advance to studies of these lowly forms of life which possess considerable advantages from a research point of view for instance with some species of fungi, all the products of any one meiosis may be recovered with ease and studied individually

The author has based his text on lectures to biochemists specialising in microbiology but the book will provide fodder for all those interested in the innermost secrets of tissue cells—from the problem of cancer to evolutionary theory

Doctors by Themselves By EDWARD F GRIFFITH, M R C S, L R C P Pp xii+614,
with 16 plates London Cassell & Co 1951 Price 21s net

This is a medical anthology containing over 800 short extracts from the writings of medical men ancient and modern The book is a wonderful miscellany on all kinds of subjects and offers a great variety of interest The extracts have been collected under five principal headings—the doctor at work, the doctor amuses himself, the doctor's troubles, the doctor looks at life, and lastly life, death and immortality, and each of these has been further subdivided so that kindred subjects are gathered together Individually, the writings are of the most varied nature There is the polite note of William Withering declining an invitation to duel, John McCrae's notes on Flanders battles, Hippocrates on sterility, Dawson's classification of the middle aged, James Lind on the scurvy, Jenner on the songs of birds and many others A most interesting and valuable collection, a wonderful bedside book and a relaxation for the leisure moment

NEW EDITIONS

Immunology By N P SHERWOOD, PH D, M D, F A C P Third Edition Pp 731,
with 8 coloured plates and 21 line drawings London Henry Kimpton 1951
Price 56s net

As in previous editions the text is written mainly for medical undergraduates but also for all those interested in immunity from a philosophical point of view. New chapters on special subjects such as Rh factors and venereal diseases will be of interest to hospital laboratory workers. As in previous editions, emphasis is laid on the practical aspect of diagnostic laboratory tests.

Discussion throughout the book deals with the underlying principles involved in infection and resistance and includes changing points of view with regard to immunity, recent ideas about vitamins, endocrines, the mechanisms of viral infection, latent infection and the new blood group factors.

The chapter on flocculation tests in the diagnosis of syphilis has been rewritten by Frank Victor and includes references to the recent work of Kahn, Kline and others. The serology of syphilis has been brought into line with the procedure details in J A Kolmer's recent publications.

The Practice of Endocrinology Second Edition, Edited by RAYMOND GREENE
Pp xxiii+389, with 56 illustrations London Eyre & Spottiswoode 1951
Price 65s

Dr Greene and his colleagues are to be congratulated on the appearance of a second edition of their excellent contribution to the *Practitioner* series within three years of its first publication. The new edition contains further illustrations of high quality and a clear and concise chapter on Diseases of Adaptation. It has been revised and brought well up to date. There is no better book for the general practitioner, or the general physician, who requires an accurate, readable and intelligent guide to modern clinical endocrinology.

X-ray Interpretation By H CECIL H BULL, M A, M B, M R C P Second Edition
Pp xxiv+406, with 287 illustrations London Oxford University Press
1951 Price 25s net

A second edition of this volume on X-ray interpretation appears after an interval of sixteen years. It is doubtful whether such a small work as this can cover satisfactorily so wide a field as radiology presents to day. Moreover, it would appear that the limited space available has not been employed to the best advantage, so that important subjects receive but scant consideration. There are no reproductions of radiographs, these being replaced by line drawings, and there are so many inaccurate or misleading statements in the text that the book cannot be recommended.

Cunningham's Textbook of Anatomy Ninth Edition, Edited by J C BRASH, M C,
M A, M D, D S C, F R C S E Pp xx+1604, with 1252 figures, many in colour
and 58 plates London Oxford University Press 1951 Price 90s net

The first edition of this work appeared in 1902 and the last in 1943. Since then numerous changes have occurred which have necessitated the introduction of several contributors who fully maintain the tradition of the work.

The present edition has been very fully revised both as to text and illustrations with the addition of the latest discoveries in various departments. This is particularly true of embryology where the material is enriched by recent researches on very early human embryos. At the end of each section a fully representative bibliography is included. The production of the book, the printing and the reproduction of the illustrations are of the highest standard. This popular textbook will continue to merit the confidence placed in its predecessors as the leading authority in the language

Edinburgh Medical Journal

April 1952

BCG-VACCINATION AS A PUBLIC HEALTH MEASURE

By ARVID WALLGREN

Professor of Pædiatrics, Royal Caroline Institute, Head of the Pædiatric Clinic, Caroline Hospital, Stockholm, Sweden

BEFORE entering into my main subject, BCG-vaccination as a public health measure, it may be desirable to say a few introductory words about this vaccination. Probably at least a part of my audience has only rather vague ideas about this procedure as this kind of measure is new in Scotland.

The vaccine contains BCG-bacilli, named from the initials of the inventors, Calmette and Guérin. These BCG-bacilli are a living but avirulent strain of bovine tubercle bacilli. In experiments on animals it has been shown that inoculation of BCG produces tuberculin sensitivity and increased specific resistance to virulent superinfections. Applied in an adequate way they produce tuberculin sensitivity also in man after a reasonable lapse of time, and follow-up studies of groups of vaccinated and non-vaccinated people have shown a significant reduction of tuberculosis morbidity and mortality in the vaccinated group. I will refer to these experiences later. The vaccination is without danger and is accompanied only by small local inconveniences. With the method mostly used, the intradermal inoculation, a papule arises after some weeks at the site of injection. It increases slowly to pea-size and may sometimes show small pustule formation. This abscess heals spontaneously after a couple of weeks and leaves a whitish scar. The regional glands may increase somewhat in size, but only exceptionally is there lymphadenitis of any significance.

Some very important principles must be followed in the practical performance of BCG-vaccination. Firstly, only those who are still tuberculin negative should be vaccinated, those who are tuberculin positive after tuberculous infection have already acquired through this infection the increased resistance that the BCG-vaccination should confer. Every individual who is going to be vaccinated should be tested with tuberculin in order to exclude a virulent infection. Negative

The Frederick Price Lecture delivered at the Royal College of Physicians, Edinburgh, 16th October 1951

tests occurring after exposure should be retested six to eight weeks later and only if the test is still negative should the inoculation be made. If this rule is not followed there is a great risk that recently acquired *primoinfection* may manifest itself before the BCG-immunity is effective. The vaccination in such cases has been of no value and may be misinterpreted as the cause of the tuberculous disease, or doubt may be cast on the efficacy of the vaccination.

Secondly, the vaccination should be performed in such a manner that tuberculin sensitivity arises. If tuberculin sensitivity is not checked after inoculation there is no proof that the vaccination has taken and immunity been produced. It is assumed that there is probably no immunity established until the vaccination has produced a systemic reaction that may be demonstrated by a positive tuberculin test. In order to avoid misinterpretations and misjudgment of the efficacy of the inoculation, exposure should therefore be prevented during this pre-immune period.

These are the principles that have been followed since BCG-vaccination was introduced in Sweden a quarter of a century ago. The same principles have been followed in the other Scandinavian countries. They have been followed also in the mass campaign against tuberculosis in the war-devastated countries in Europe and undeveloped states outside Europe. In this Joint Enterprise of the Scandinavian countries, WHO and UNICEF, about 17,000,000 persons were vaccinated. Experience with the practical performance of BCG-vaccination under various conditions is thus very great.

What can be expected from the prophylactic effect of the vaccination? From a theoretical point of view one ought to expect the same kind of immunising effect as results from a well tolerated virulent tuberculous infection. The latter produces a specific resistance against superinfections. It is very seldom that superinfection in a tuberculin positive individual causes any harm. BCG-immunity is without doubt weaker than that which follows a virulent infection and it may be more easily overcome. The immunity makes itself shown even in such cases, however, by diminishing the pathological effect of the virulent infection, it is seldom that we see a severe clinical primary tuberculosis in those who have acquired BCG-immunity before infection.

The immediate pathological effect of a virulent infection is thus in high degree neutralised by the BCG-immunity. This immediate consequence includes not only primary tuberculosis, but also military tuberculosis and tuberculous meningitis, and both these malignant tuberculous diseases may to a very great extent be prevented by BCG-vaccination. In none of the Scandinavian countries has a case of these malignant disseminated forms of tuberculous disease been seen in an adequately vaccinated person.

According to reports from several quarters, post-primary pulmonary tuberculosis arises more frequently in persons with marked primary tuberculosis than in persons who show insignificant or no reaction

in the lungs after airborne virulent primary infection. Because BCG-vaccination to a great extent prevents severe primary tuberculosis it is possible that it also diminishes the risk of acquiring post-primary pulmonary tuberculosis later. As will be seen from the slides that I will show in a few minutes theoretical speculation corresponds to practical experience.

In summary it may be said that an adequately performed BCG-vaccination produces specific immunity that is sufficiently strong to protect to a great extent against severe primary tuberculosis, miliary tuberculosis and tuberculous meningitis and to a certain extent, also, against pleurisy and post-primary pulmonary tuberculosis. The morbidity and mortality rates of tuberculosis have been at a marked lower level in all reports of follow-up studies of adequately vaccinated groups of people as compared with tuberculin negative non-vaccinated groups. It may be said, however, about most of these studies, that the way in which they were performed is not above criticism, and the conclusions drawn have not always been correct. The reliability of the results can not therefore always be taken for granted. I will only quote a few of the more recent and, according to my judgment, more reliable studies.

The first report of the effect of the vaccination in school-children in the Swedish antituberculosis campaign in Rhineland-Westphalen in Germany (1948-49) has just been published. Out of 11 million tuberculin-negative children, 400,000 were vaccinated, while in 700,000 the offered vaccination was not accepted. Only 5 children in the vaccinated group fell ill with tuberculosis = 0.012 per thousand, and only 3 of them contracted tuberculous meningitis, = 0.007 per thousand. The corresponding figures in the non-vaccinated group are 131, = 0.187 per thousand, and 71, = 0.101 per thousand. The conclusion drawn is that the incidence of tuberculous disease is about 15 times greater in the non-vaccinated group (Fig. 1).

I may refer to Dr Tornell's report from a small Swedish town as an example of the value of BCG-vaccination in combating tuberculosis in a community. Of those who had been exposed to tuberculous infection after the establishment of the BCG-immunity, 82 cases in each 1000 years of observation contracted tuberculous diseases, while of the non-vaccinated exposed tuberculin-negatives there were 136 cases for each 1000 years of observation (Fig. 2).

The results of the vaccination in the Swedish army, reported by Difs and Dahlstrom, are very interesting. In 1941-44 25,239 tuberculin-negative conscripts were vaccinated and 36,235 remained unvaccinated. One must remember that the sources of infection were not immediately eliminated at the beginning of the military service and that those vaccinated might have been exposed to virulent infection during the incubation period of BCG, as it takes about six weeks for the vaccination to be effective and about the same time for the tuberculous infection to manifest itself, the full effect of the protection could not

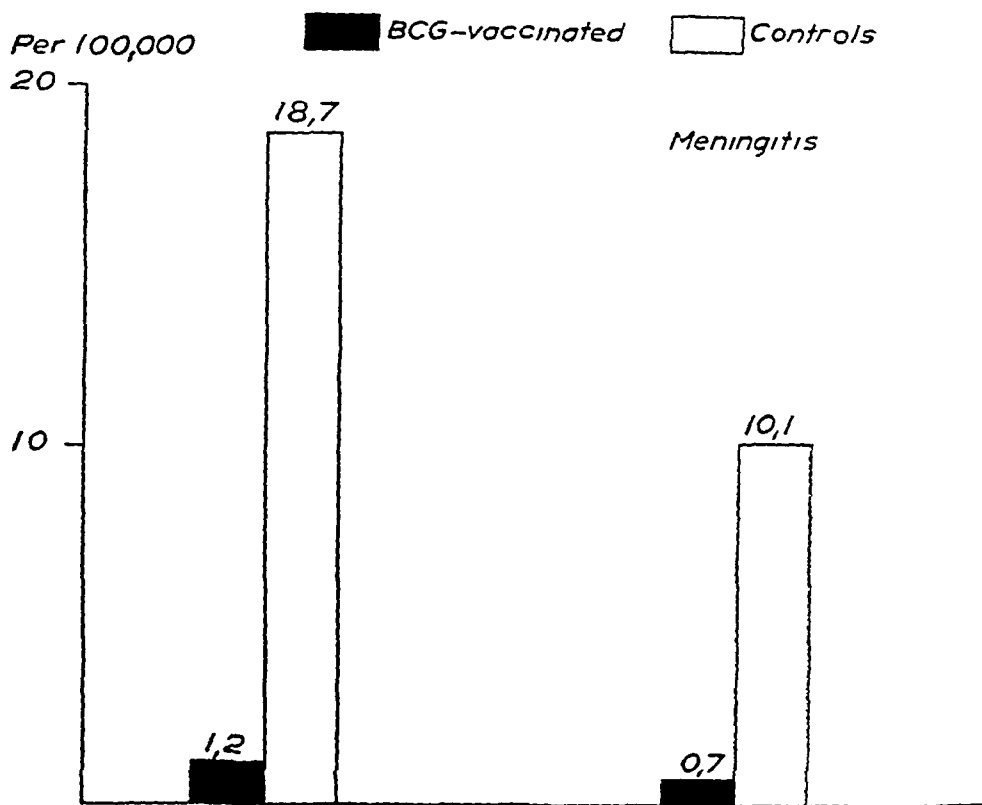


FIG 1—Germany Disease in 400,000 BCG vaccinated and 700,000 Non vaccinated School children

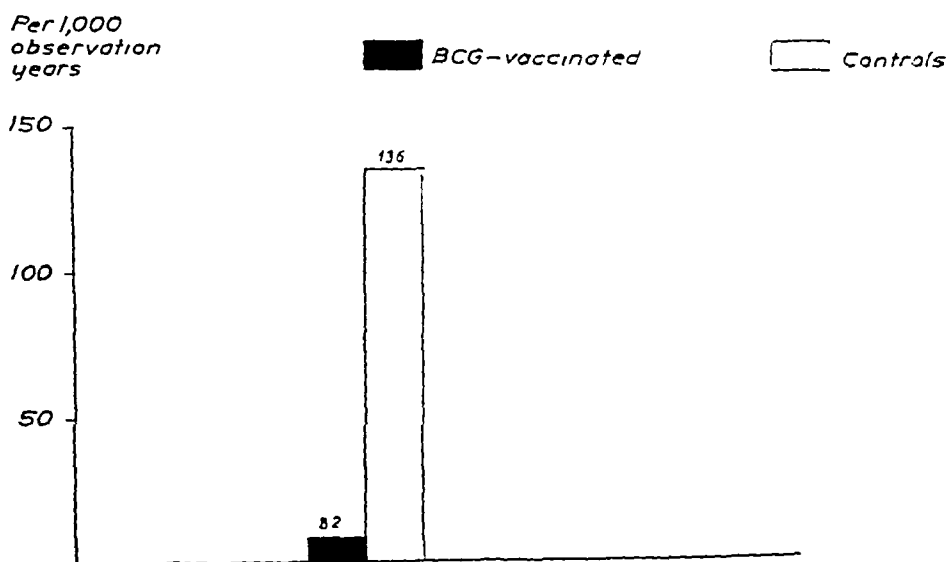


FIG 2—Sweden Tuberculous Disease in BCG vaccinated and Non vaccinated Groups of the Population (Tornell) per 1000 Observation years

be expected until after three months (Fig 3) At a follow-up study in 1946 the following incidence of different kinds of tuberculosis were found —

Number of months after vaccination		0 2	2 4	4 6	6 8	8 10	10 12	more than 12
Primary tuberculosis	Vaccinated	27	14	2	4	1	5	5
	Non vaccinated	34	22	15	19	10	13	27
Pleurisy	Vaccinated	6	13	19	7	9	5	17
	Non vaccinated	3	12	8	22	6	19	45
Destr pulm tub	Vaccinated	3	0	1	0	0	0	5
	Non vaccinated	1	0	1	0	4	1	19 ²

The experience of the Danish school-physician Hyge has often been quoted because the conditions correspond closely to those of a laboratory experiment The 12-18 year-old children were tested with tuberculin and the non-reactors (200) were offered BCG-vaccination One hundred and six accepted the vaccination During two months the children were exposed to accidental tuberculous infection from a

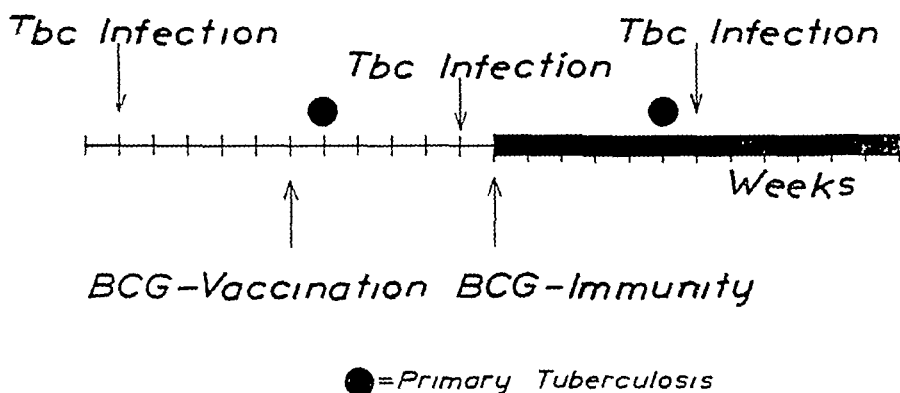


FIG 3

deputy teacher, and the effect of the ensuing epidemic was reported by Hyge three years later Two of the 106 BCG-vaccinated girls had mild pulmonary tuberculosis and 41 of the 94 non-vaccinated tuberculin negative girls acquired tuberculous diseases, 6 of them had to be treated by pneumothorax and 1 of them died The morbidity rates were 1.9 and 43.6 per cent respectively In the spontaneously tuberculin positive group the rate also was 1.9 (Fig 4)

Since 1926 Heimbeck has vaccinated pupil nurses on a voluntary basis in Oslo In 1948 he checked the morbidity and the mortality rate in the two groups of vaccinated (501) and non-vaccinated (284) tuberculin negative nurses In the first group the morbidity rate was 9.9 and the mortality 1.0 per 1000 observation years, compared to 41.4 and 4.7 respectively among the unvaccinated (Fig 5)

The experience of Aronson and Palmer in the U S A is perhaps of

■ 105 tuberculin-positives, 315 obs years, 2 sick, 0 dead in tuberculous
 ▨ 106 BCG-vaccinated, 318 obs years, 2 sick, 0 dead in tuberculous
 □ 94 controls, 282 obs years, 41 sick, 1 dead in tuberculous

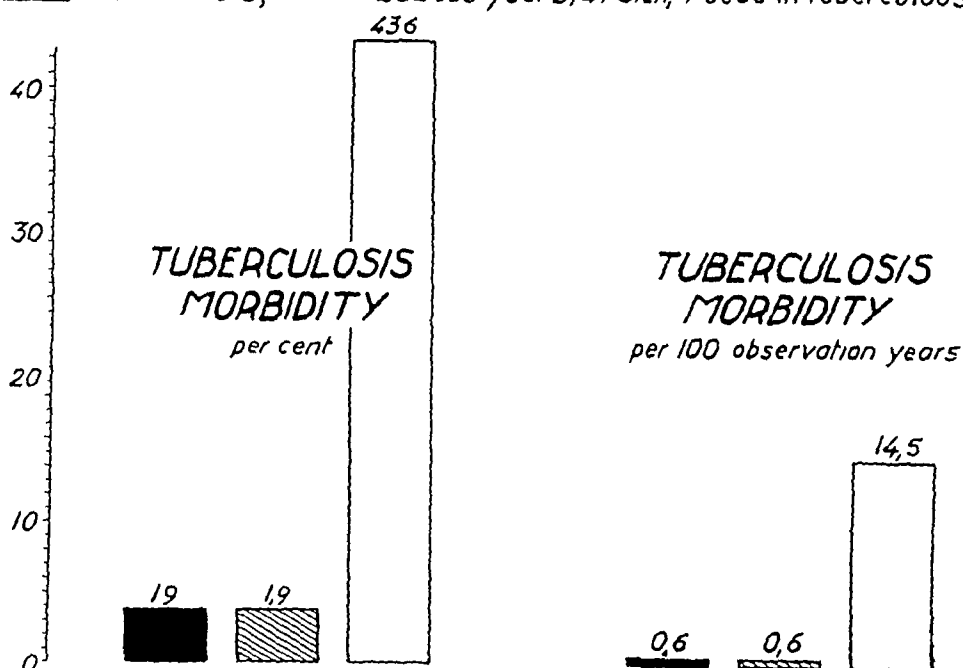


FIG 4—Hyge 1947 (Highschool—Girls)

■ 668 tuberculin-positives, 7449 observation years
 ▨ 501 BCG-vaccinated, 7449 observation years
 □ 284 tuberculin-neg controls, 2563 observation years

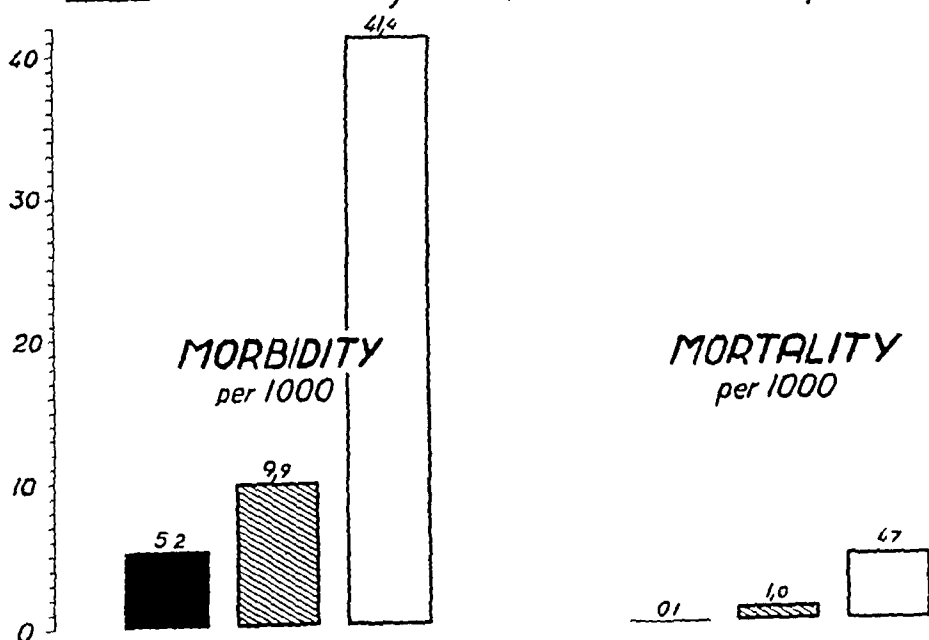


FIG 5—Heimbeck 1948 (Pupil nurses)

special interest from a public health point of view. In 1935-38 they tuberculin-tested Indians aged 1-20 years on several reservations and found 3000 non-reactors. They injected BCG in half of this group and saline solution in the rest. In 1948 a follow-up-study showed that the morbidity rate in the vaccinated group was 40 or 0.4 per 1000 observation years and $185 = 3.4$ per 1000 observation years in the non-vaccinated group (Fig. 6).

In none of the hitherto reported follow-up studies has the incidence of tuberculosis been equal or less in a non-vaccinated group. Most

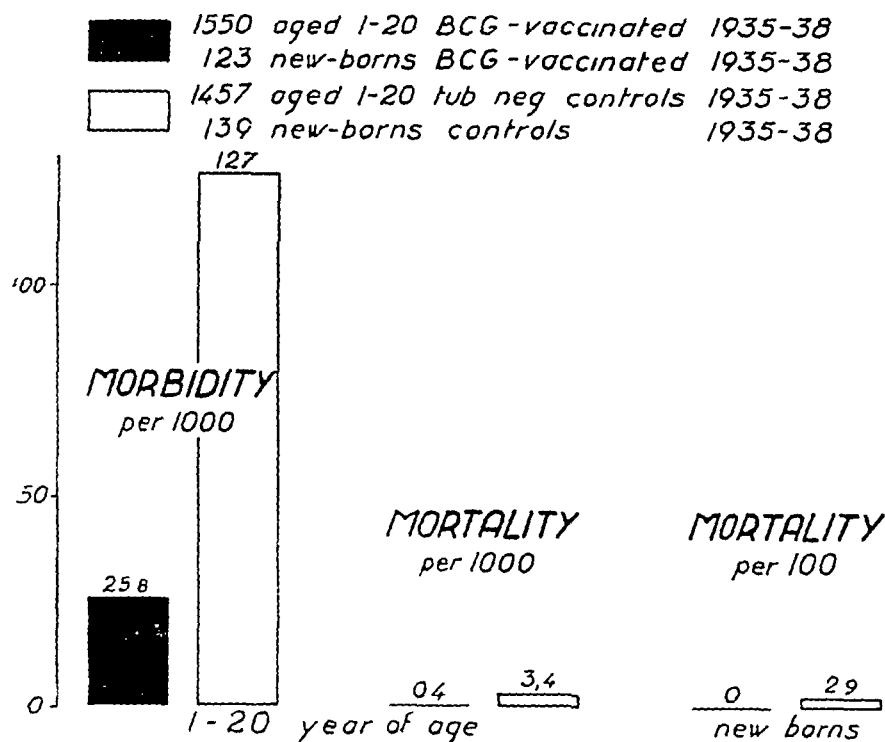


FIG. 6—Aronson 1948 (Indians)

observers are therefore of the opinion that BCG-vaccination has proved its immunising effect and ought to be accepted as public health measure against tuberculosis.

If the health authorities in a country intend to introduce BCG-vaccination as a means of combating tuberculosis the question may arise if this should be done on a voluntary or compulsory basis. When other used and accepted measures are compulsory, for example notification of new cases, examination of family contacts, pasteurisation of market milk, why should not BCG-vaccination also be made compulsory? As a matter of fact this has been done in some countries, among others Norway, France, Yugoslavia and Turkey. Most public health authorities have, however, kept BCG-vaccination on a voluntary basis, while trying to educate the public to accept it. The effect of

BCG-vaccination as a public health measure cannot be compared to that of smallpox vaccination and its value is still disputed in some quarters

The experience of a quarter of a century has shown that BCG-vaccination is quite without danger. However, the inconvenience of the abscesses that are produced exceptionally and never can be prevented with absolute certainty would probably be exaggerated if they occurred in an individual who did not want to be vaccinated. The effect of vaccination could be misinterpreted and counter propaganda might be started. This is especially true in west-democratic countries in which the population is accustomed to make its free choice in most matters. In these countries enlightenment and propaganda ought to be sufficient and give satisfactory support to BCG-vaccination. If the effects of the vaccination are as striking as they have been in the Scandinavian countries, there ought to be no difficulty in persuading threatened people to have themselves vaccinated.

The relativity of the protection that a BCG-vaccination affords also makes the introduction of compulsory BCG-vaccination in the public health scheme undesirable. Even the immediate pathological effects of primary infection cannot be prevented with certainty, and protection against the very important late post-primary forms of tuberculous disease is still less certain. Reluctant people cannot be told that if they have their children vaccinated it will keep them free from tuberculosis. Against the spread of tuberculous infection in a community BCG-vaccination is of small immediate effect as the primary tuberculous disease that may arise in unvaccinated persons seldom constitutes a source of infection. For the sick individual and his family the sickness is a tragedy, but from a public health point of view it is of less immediate importance.

One must also always weigh the degree of risk that a person runs against the nature of measures to be taken against this risk. The risk depends on two different factors: the danger of infection and the possibility of the infection becoming dangerous. The risk of infection must in general be regarded as very small in a community with low tuberculous morbidity and mortality. In such a community there are few ambulatory sources of infection and therefore small danger of becoming infected. Out of 1000 tuberculin negative individuals perhaps only one will acquire the infection annually. One must unnecessarily vaccinate 999 persons in order to give relative protection to 1.

In a community with a high tuberculous morbidity, with numerous sources of infection, many of which cannot be controlled by the public health service because they are still undetected, the risk of tuberculous infection will be very great. Out of 1000 such persons of such a community perhaps 500 will be infected within a couple of years. Vaccination of tuberculin negative persons gives obvious results and the gain in health of the population more than compensates for the

time and trouble spent on vaccination. In communities that from a tuberculous prevalence point of view occupy an intermediate position between the mentioned two extremes, the risk varies with the degree of tuberculous morbidity, and with it the necessity of BCG-vaccination. This is true for most communities.

The risk of infection is, of course, not equal for every member of the community. The degree of the risk depends on the environment in which the individual lives or works—whether or not there are any sources of infection which cannot be avoided. Tuberculin negative members of tuberculous families and medical and nursing personnel in hospitals where consumptives are treated are probably the groups most threatened with being infected in the near future. These groups need every kind of protection and they ought to be the first to be BCG-vaccinated in a community that intends to introduce this method in its public health service scheme. There are some other groups that are more or less on the same level as the above-mentioned in regard to the degree of risk of infection, dentists, personnel in shops, banks and post offices, *z.e.* people who in their profession must come in close contact with many people, among whom there may be consumptives.

From quite another point of view those engaged in certain other occupations constitute groups for whom an improved protection against tuberculous infection is especially desirable: those belonging to the military forces and the crews of cargo and passenger ships. The risk of being infected may not be greater than in the population in general, but the consequences of primary infection, sickness and loss of working capacity, may be of much greater immediate importance. When these groups fall ill and become bed-ridden they cannot be immediately replaced. If many soldiers in a division acquire tuberculous disease and have to be at least temporarily discharged from the military service the effective force of the division is decreased. If many able seamen or firemen of a merchant ship's crew fall ill, the ship may be too short of hands to manœuvre satisfactorily. It would therefore be prudent to prevent or to lessen the sickness hazard by BCG-vaccinating those who are tuberculin-negative at the beginning of the military service or when enlisting as members of a ship's crew. There are other professions in which it may prove especially difficult to get competent deputies in the event of sickness, for instance, teachers.

Another factor is also to be considered when it is a question of vaccination on a voluntary basis: namely the degree of facility and convenience in performing the vaccination. The necessary preparation and examinations before and after inoculation, tuberculin testings, segregation of the person to be vaccinated, if necessary, and the inoculation itself, demand many visits. Under certain circumstances this inconvenience is minimised, namely when the individual to be vaccinated, is hospitalised or otherwise kept under continuous medical control.

This is the case with new-born babies in maternity hospitals, school children, conscripts and children living in various kinds of child institutions. The newborn babies at the lying-in hospitals are seen daily by the nurses and/or doctors and it causes very little trouble to inoculate them. Pre-vaccination tuberculin testing is not necessary. In countries where most deliveries take place in maternity hospitals the first BCG-vaccination is more and more often performed in the newborn babies. In Stockholm, for instance, children are only exceptionally born at home. More than 90 per cent of all newborns are BCG-vaccinated at the maternities. It is easy to perform the necessary tuberculin control of the vaccinated infants if they are regularly supervised by a welfare centre. The tuberculin tests can be performed there and read by the nurse during home visits.

In all progressive countries school children are regularly controlled by the school health services. In some countries tuberculin testing is routinely made on school children. It is an easy task to inoculate the tuberculin negative ones with BCG and to control the BCG-vaccination by new tests some months later. In our country tuberculin testing is performed at least twice during the school years, once when the child starts school at 7 and then when he is ready to leave school at 15 years of age. In connection with this tuberculin testing those who are still negative are offered BCG-vaccination. The parents are informed about the value of BCG-vaccination, their consent to perform the vaccination is requested, and usually is readily given. It is especially important to give the increased resistance that a BCG-vaccination can afford to a tuberculin negative adolescent, who is about to leave school and perhaps also his parents' home in order to continue his studies elsewhere or to learn a profession. He may move from an almost tuberculosis free community to a city with a high incidence of tuberculosis. The exposure risk in the new environment, over which the parents have no control, may be much greater than in the old one. In addition, there is increased susceptibility to the more severe forms of primary tuberculosis at this age.

Conscripts are examined when they start military service, and their state of health is continually supervised by medical officers. Tuberculin testing and microradiography of the chest should be constituents of the medical examination. It is an easy task to inoculate BCG in the non-reactors and to test if the vaccination has taken afterwards. In our country this has been in effect since 1940 and at present more than 50 per cent of the non-reactors accept the vaccination. Partly due to their susceptible age, partly to the change of environment and the hard military training, the conscripts probably run a greater risk of being infected and of acquiring a more severe form of tuberculosis than the population in general. Especially in the beginning, before the group has been duly examined and those who are sick excluded from service, some of the reactors may suffer from hitherto unknown and undetected destructive pulmonary tuberculosis. These conscripts

constitute dangerous sources of infection for their tuberculin negative mates. As has already been stressed, there may be some cases of tuberculous disease manifested among the vaccinated non-reactors within the first two to three months of the military service, because the immunity is not established until six to eight weeks after the inoculation. Therefore the rational thing to do is to vaccinate the future conscripts before enlistment in order to provide them with the increased resistance offered by BCG-vaccination.

All hospitalised patients, for example expectant mothers in the maternities, and children in children's hospitals, as well as all inmates of institutions, such as children in day-nurseries and play-schools, are subject to medical control. Tuberculin testing and BCG-

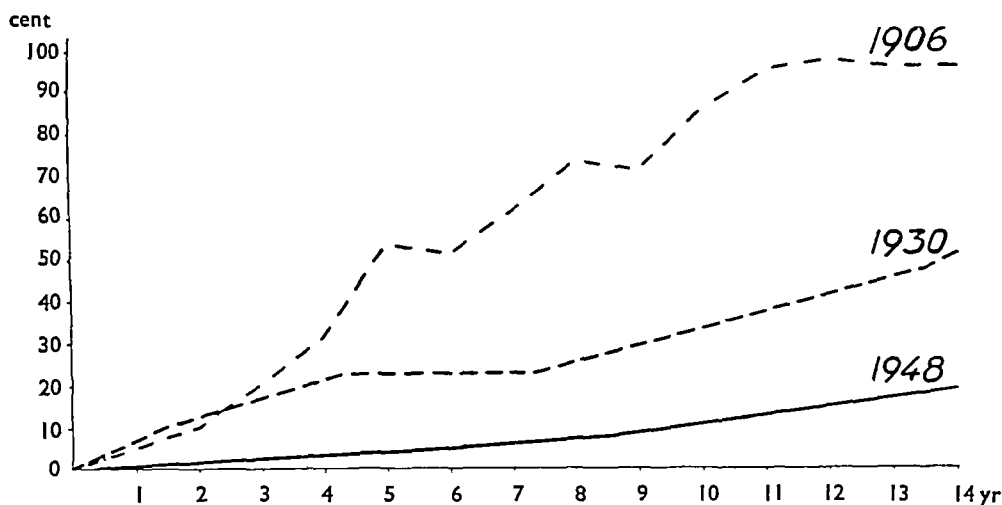


FIG 7—Incidence of Tuberculosis Infection in Childhood

inoculation in those who are non-reactors can easily be performed at the visit of the physician or the visit of the child.

The degree of the risk of primary infection also depends on the susceptibility of the individual which varies a great deal. It is, for instance, different in varying age groups as is shown by this diagram (Fig 7). The direct pathological lesions of primary infection are usually benign. It is only exceptionally that the most common type of primary tuberculosis, that in the lungs, progresses to a fatal termination. Other localisations of primary tuberculosis seem to be still more benign. Death from primary tuberculosis is as a rule due to acute disseminated forms of the disease, miliary tuberculosis and tuberculous meningitis. The mortality rate of primary tuberculosis reflects thus the incidence of the latter two tuberculous diseases, this holds true even to-day with the improved prognosis due to streptomycin treatment.

From the mortality rate in different age groups it can be seen that the worst prognosis of primary infection is in infants and young children. The mortality rate then declines and reaches its lowest

point at about 10 years of age and later increases somewhat at puberty (Fig 8) Now the mortality curve does not indicate the degree of danger of a primary infection in different age groups unless it is contrasted with the incidence curve of the infection This well-known curve shows that very few infants are infected and that the incidence increases slowly and reaches its peak at about 40-45 years of age Thus, at an age with the smallest number of infected, the number of those dead with primary tuberculosis is highest, and at an age with about 100 per cent infected the mortality rate is almost nil This must mean that

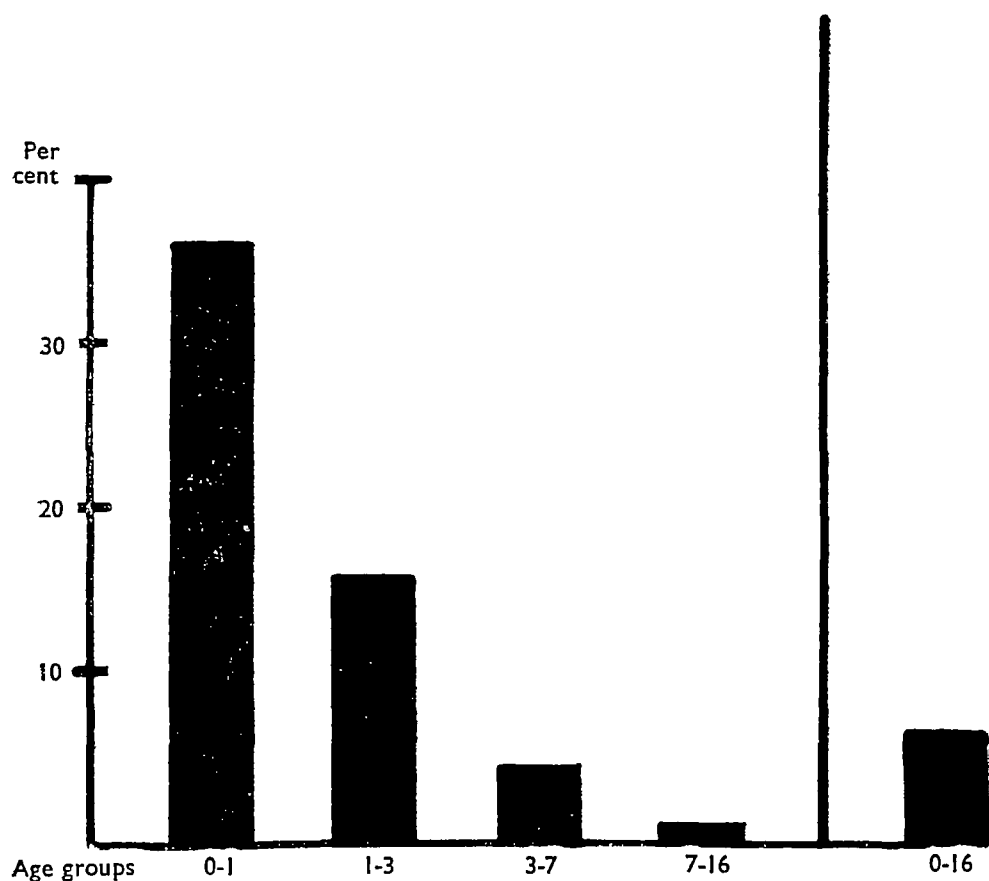


FIG 8—Mortality Rate from Tuberculosis in different age groups

the younger the child the more dangerous is the primary infection, and that the danger increases somewhat again at the age of puberty The figures of the percentages may vary from one country to another, but the trend of the mortality and type of the infection incidence curves is the same everywhere From this one may conclude that the most susceptible individuals in the population are infants, small children and young people at puberty From a public health point of view it should be regarded as important to diminish the greater risk of tuberculous infection these age groups run by increasing their resistance This can be accomplished by BCG-vaccination

Now the importance of primary tuberculosis cannot be evaluated solely on the basis of the mortality curve The morbidity also plays

a significant role. This seems to be neglected or at least underrated by some authors. Nobody knows the exact incidence of clinical primary tuberculous disease after the first infection, but the morbidity is of course much higher than the mortality. In our own experience the morbidity is apparently greater in the youngest age groups than in the oldest ones. It is rare for an infant or very small child to escape a clinical primary tuberculosis after infection, and it is rather unusual for an individual at 30-40 years of age to fall ill with this disease after having acquired the first infection. The only possible way to get information about the morbidity rate is to follow the fate of non-reactors until they have acquired their first infection and then to examine them carefully by X-rays, temperature measuring, sedimentation test, gastric lavage test, etc., in order to find out the immediate consequences of the first infection.

If one judges from reports, the incidence of clinical primary tuberculosis seems to vary considerably in different countries. In Central Europe and the Scandinavian States it is a very common disease, while in some North American states, for instance, Minnesota, it is a very rare illness. It is only in countries where primary tuberculosis is frequent that it becomes a public health problem.

Even if primary tuberculosis in adults is not dangerous, it is nevertheless of importance because its manifestation means loss of working capacity for some months with resultant loss of income, social consequences, etc. It is evident that it is of interest not only for the family but also for the community to prevent these sequelæ of a primary infection in individuals of professional age. In school children and university or vocational students it may mean loss of study capacity and difficulty in keeping up with the teaching programme.

The duration of the effect of a public health measure is of great importance, it must not be too temporary. In this respect the duration of BCG-immunity is of great interest. So far our knowledge about this matter is rather poor. It is difficult to study this question because we have no reliable test on immunity in human beings. In practice we use the tuberculin test to judge whether BCG-vaccination has been effective or not, but this is not a reliable test of immunity as sensitivity to tuberculin and specific resistance to tuberculosis are not identical, one can exist without the other and they do not necessarily run parallel. Tuberculin tests are, however, the only means of telling if BCG-vaccination has led to the expected general change of mode of reaction in the inoculated individual. From experiments on animals with inoculation of living tubercle or BCG-bacilli it is known that the tuberculin sensitivity is demonstrable about the same time as immunity. In practice we consider a person immune to tuberculous infection if he is tuberculin positive and we apply the same test when it is the question of BCG-vaccinated persons. This is, however, an assumption and may be wrong in exceptional cases.

Another factor that makes it very difficult to determine the duration

of BCG-immunity is the ever-present possibility of virulent superinfection. When a BCG-vaccinated person acquires a primary tuberculous infection this does not as a rule produce any immediate clinical signs, partly, at least, thanks to BCG-immunity. The virulent superinfection produces in its turn specific tuberculosis immunity, which is doubtless far stronger and more durable than immunity after BCG-vaccination. The weak BCG-immunity has thus been transformed into a strong specific tuberculosis immunity. If one tests such an individual with tuberculin it is not BCG-immunity but naturally acquired tuberculosis immunity that is tested. Now most people in a community live in environments such that the occurrence of accidental virulent infection cannot be excluded with certainty.

There are no reliable means of differentiating the tuberculin sensitivity produced solely by BCG-vaccination from that produced by virulent superinfection. Usually sensitivity is much stronger after virulent infection, but the sensitivity after BCG-inoculation sometimes becomes gradually very marked. Probably most students of this question agree with Herzberg's opinion that a sudden increase in tuberculin sensitivity, that remained low for a long time after BCG-inoculation, indicates the occurrence of a virulent superinfection. It is not often that one has the opportunity to control tuberculin sensitivity after BCG-vaccination with sufficient frequency and regularity to aid in elucidating the problem of the duration of BCG immunity. Usually we cannot determine whether or not a virulent superinfection has occurred. We consider all BCG-vaccinated persons who are still tuberculin positive as being BCG-immune, unless it is obvious that they have been exposed to and acquired a virulent infection. In general, this judgment ought to apply, but single cases may be misinterpreted. The evaluation of the duration of BCG-immunity by tuberculin tests must therefore be accepted with some reserve as a method used only because we lack other more reliable tests.

Experience has shown that the duration of tuberculin sensitivity after BCG-vaccination, in people evidently not exposed to tuberculous infection, varies in individual cases. Sensitivity may exceptionally disappear after only one year or less or it may still be present ten years or more. In general one may say that it lasts about five years or more in three-quarters of all intradermally vaccinated children. As it is not possible to foretell the duration of tuberculin sensitivity in an individual case, this must be examined by repeated tuberculin tests. If the tuberculin test is negative, the immunity is considered lost, too, and in such individuals the BCG-vaccination is no longer active. If the test is positive, the immunity is regarded as present, but will have to be checked again after some time. Sooner or later probably all BCG-vaccinated persons who have not been virulently infected lose their tuberculin sensitivity and artificial immunity.

A question of practical consequence is, when and how often the tuberculin test should be made? It may happen that the test turns

negative six to twelve months after it was last found positive. Theoretically it would be best to control the tuberculin sensitivity at least every year, but this is possible only occasionally. In groups who run a great risk of exposure, for instance, nurses and medical men, annual control is especially indicated, but it is not possible in all vaccinated people. One has to choose the middle path between what is desirable and what is practicable. Exactly where this is is not generally agreed upon.

The problem often solves itself by the facility with which tuberculin testing can be performed. I refer to the groups mentioned earlier: newborns, infants, pre-school children in institutions, children at the beginning and end of school-age conscripts, women in maternity hospitals, institutionalised and hospitalised persons.

If the examination is performed in the newborn period, the first checking of tuberculin sensitivity may be performed in the first school-year or earlier if the child attends a pre-school institution, the second checking at the end of the school-age, and the third in military service. In the meantime it may be performed occasionally in connection with hospitalisation. As regards special threatened groups of the population the checking ought to be made at shorter intervals. That it is possible to proceed in the way mentioned here is shown by experience in our country, where this schedule is followed.

Tuberculin testing ought to be sufficiently exhaustive to exclude any remaining sensitivity. There is no general agreement about this question, the problem is solved according to personal experience and other influencing factors. Usually a negative Mantoux test of 1 milligram O.T. is considered sufficient to exclude tuberculous infection, and the same strength is often used to exclude remaining tuberculin sensitivity after BCG-vaccination. To use 1 mg. as the first and only test may, however, be dangerous and produce local necrosis of the skin since one can never predict the presence or degree of any remaining allergy. One must start with weaker tests and proceed to stronger ones if the former prove negative. This means that several tests often have to be performed, an inconvenient and time-consuming procedure. For practical purposes a middle course must be followed in this problem also. One has to use as simple and few tests as possible and to disregard the possibility that they are not 100 per cent reliable. Even if one cannot prove with certainty that all tuberculin sensitivity is lost by this procedure, it is sufficiently reliable to exclude remaining sensitivity that may produce local or systemic inconveniences upon re-vaccination.

The simplest procedures are the ointment or patch-tests, and they are generally used as the first tests. In mass examinations of children they are often the only test employed. In adults with their thicker and less sensitive skin, this method is unreliable. The scarification test (Pirquet test) with concentrated tuberculin and often with added adrenalin is used instead in some quarters. This is followed eventually by a Mantoux test, 0.1-0.5 mg. The latter may be preceded by a

weaker Mantoux test, 0.01 or 0.05 mg. In our schools and in the military service examinations an ointment or patch-test is used first and if this is negative we continue with 0.5 or 1 mg. Mantoux. We may proceed from ointment test through Mantoux 0.1 to Mantoux 1 mg.

Even with a Mantoux 1 mg. negative, a certain degree of tuberculin allergy remains, shown by the type of local reaction after re-vaccination in such cases. This slight allergy does not cause any inconvenience. It probably is a sign that BCG-immunity is fading and that a booster inoculation is needed. If the reasons for the primary vaccination still exist, re-vaccination should be performed and the checking of tuberculin sensitivity made as before.

The introduction of BCG-vaccination on a wide scale is admittedly of some inconvenience from a public health point of view. It makes the checking of the spread of tuberculous infection and the diagnosis of tuberculous diseases more difficult by the production of artificial tuberculin sensitivity. Tuberculosis is, however, not only diagnosed by means of a positive tuberculin test, but also by X-ray of the chest, gastric lavage bacilloscopy, sedimentation test and other less specific clinical signs and symptoms. It is the synthesis of these tests that confirms or denies the suspicion of tuberculous disease. In one extensive experience in the diagnosis of tuberculous disease in BCG-vaccinated persons, it has only been in exceptionally rare cases that the diagnosis could not be established, and it has never happened that this failure had any unfavourable consequences for the patient. The elimination of tuberculin testing as a diagnostic procedure in tuberculous diseases should not therefore be considered so important from a public health point of view as to prevent the introduction of BCG-vaccination.

The inconvenience of being unable to check the incidence of tuberculous infection in a BCG-vaccinated population is of greater importance. This is, however, mostly in regard to statistics, the changes in the prevalence of tuberculous infection in different age groups and at different periods of years cannot be determined. For the public health service, changes in incidence of tuberculous morbidity and mortality are of far greater interest and these two registered subjects can be recorded equally well in a BCG-vaccinated population. In such a population the morbidity as well as the mortality of tuberculosis should be and are greatly reduced. One has thus to make a choice between increased difficulty in registering the spread of the tuberculous infection and a notable reduction in the registered number of tuberculous diseases and deaths from tuberculosis. This choice should not be a difficult one for the public health service (Fig. 9).

BCG-vaccination is no panacea which is in itself sufficient to abolish tuberculosis in a community, an opinion which might perhaps have arisen as a result of an exaggerating propaganda. BCG-vaccination is only one part in the scheme of the anti-tuberculous campaign. Other measures are more important, namely measures aiming at

preventing tuberculous infection, at increasing the natural resistance of the population by a satisfactory standard of living, at the early detection of tuberculous disease and giving everyone in need of it adequate treatment. When this programme is effective, primary infection is postponed from early childhood to older age groups but at present almost everyone is going to be infected sooner or later. The object of BCG-vaccination is to produce artificial specific immunity in those who still are un-infected. As we never can tell with certainty

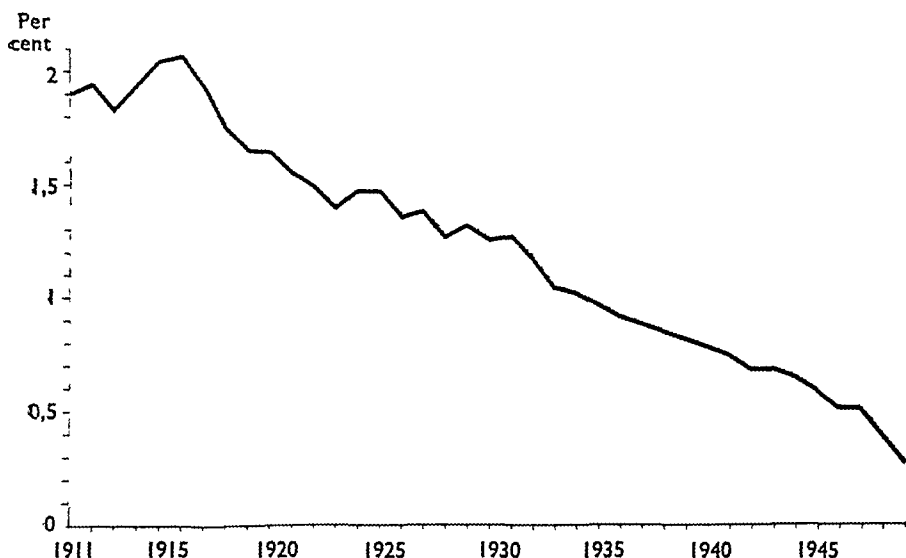


FIG. 9.—Tuberculosis Mortality Rates in Sweden

when the primary infection may occur and who is going to be infected, the earlier artificial immunity is established the better. In a country with high incidence of tuberculosis a general vaccination of children of the youngest age groups is preferable as a public health measure. If births generally take place in maternity hospitals the BCG-vaccination is most conveniently performed on newborns without any preliminary tuberculin testing. By tuberculin control and revaccination if necessary, the virulent infection, when and if it occurs, is generally prevented from producing clinical primary tuberculosis and early post-primary disease. In persons of all age groups running evident risk of exposure, *e.g.* children in tuberculous homes and hospital personnel, BCG-vaccination should as a public health measure be performed in those still tuberculin negative. In addition all other known and available measures of exposure and disposition prophylaxis should be applied at the same time.

THE DETERMINATION OF BACTERIAL SENSITIVITY TO ANTIBIOTICS

By J C GOULD, B Sc, M B, Ch B, and J H BOWIE, M B, Ch B

*The Departments of Bacteriology, the University and the
Royal Infirmary, Edinburgh*

INTRODUCTION

THE need for a simple, expeditious and reliable *in vitro* technique for the determination of the sensitivity of bacteria to antibiotics becomes more essential with the ever-extending use of these drugs

Technical simplicity is essential since requests for these tests are becoming numerically formidable and their value to the clinician depends greatly upon the rapidity with which they can be performed

Realising four years ago that one of the main factors in successful chemotherapy is speed in preliminary bacteriological investigations, one of us (J C G) began to use impregnated filter paper discs implanted on inoculated culture plates as suggested by Morley (1945) and Kolmer (1947). The method is now widely used and many modifications have been developed

The purpose of this paper is to describe the techniques evolved in this department to cover all the antibiotic work required in the hospital. We believe the results are adequate for clinical purposes. In the preliminary bacteriological reports emphasis is laid upon sensitivity rather than species identification, and with most specimens a statement of the organisms present and their sensitivity, relative resistance, or resistance can be made within twenty-four hours. Technical procedures have been simplified and standardised as far as possible so that the results are reliable, easily reproducible, and tedious daily controls are eliminated. Moreover, the results are unaffected by minor variations in technique.

The use of absorbent paper as a means of carrying penicillin solutions on the surface of solid media for diffusion purposes appears to have been first suggested by Pope in 1940 (Heatley, 1944). A few years later when methods of assaying penicillin were being explored a number of investigators adopted absorbent paper discs in place of formerly used methods (Lamanna and Shapiro, 1943, Foster and Woodruff, 1943, De Beer and Sherwood, 1944, Sherwood, 1944, Epstein, 1944, and Vincent and Vincent, 1944).

Filter paper is the most convenient form of absorbent paper likely to be of uniform quality and for this reason has been used by most workers. Uniform quality is most important because the great advantage of paper discs is that each absorbs the same amount of fluid if they are of the same size.

As used both in sensitivity determination and in assay, the filter-paper disc method is simply a form of diffusion technique (Sherwood,

1944) As with the other standard diffusion techniques such as the "cup-plate," "ditch-plate" and "cylinder-plate" methods it is affected by certain factors (Vincent and Vincent, 1944, Loo, 1944, Schmidt, 1944, Hobby, 1942) such as the pH , the thickness and state of hydration of the medium and by the lag phase of the test organism. However, the disc method appears to be less subject to these variable factors than the other methods (De Beer and Sherwood, 1944, Sherwood, 1944, Vincent and Vincent, 1944, Sherwood, 1947) and undoubtedly has definite advantages over them in the ease with which the discs can be prepared and stored, the increase in accuracy due to the amount of fluid which each will absorb, the even and constant contact of the disc with the medium, and the simplicity of the technique which allows replicate tests to be rapidly set up, also the convenience with which the plates can be handled.

MATERIALS

Preparation of the Paper Discs—Throughout this work, Whatman No. 1 filter paper was used. The discs were cut out of sheets of the filter fabric with a paper hole-puncher having a diametral size of 7 mm. The discs so produced are fractionally less than 7 mm in diameter and vary insignificantly in size as long as the instrument is sharp and single thicknesses of paper are punched, single sheet punching also ensures that the discs remain discrete and are more easily handled.

The discs are counted accurately into lots of 100, and put into 1 oz. screw-capped wide-mouthed containers. These bottles are then sterilised in the hot-air oven at $150^{\circ}C$ for one hour.

Preparation of Antibiotic Solutions and Impregnation of the Discs—The solutions are prepared with sterile distilled water and commercial preparations of high standard issued for clinical use. One ml. of the required solution is then added to each bottle of 100 discs, and as the entire volume is absorbed we may assume that each disc takes up approximately 0.01 ml. Thus dilutions of the antibiotics are prepared to contain, in 1 ml., 100 times the quantity required in each disc. The amount of each antibiotic per disc is as follows—

TABLE I
Amount of Antibiotic per Disc

Penicillin	Streptomycin	Terramycin	Chloromycetin	Aureomycin
1 unit (0.66 μg)	10 μg	10 μg	25 μg	50 μg

The discs are used wet. The bottles may be stored in the refrigerator at $5^{\circ}C$ and the antibiotics will retain their potency for at least three months. Before use the bottle should be shaken to distribute the discs around the walls of the container and this allows them to be picked up more easily with forceps.

The discs are transferred to the inoculated plates with a pair of fine-pointed tweezers. The tweezers may be kept with their tips immersed in 70 per cent alcohol which is flamed off before use. The tips of the instrument should be flame-sterilised between each transference to prevent contamination, but even without this precaution the contamination rate of the discs is surprisingly low. When it does occur organisms of the *Proteus* Group are the common offenders.

The Standard Organism —The standard organism used for all the assays and for the preparation of the standard graphs for each antibiotic was a *Staphylococcus aureus* (S5). This organism has the following sensitivity values as calculated by the recognised procedures —

TABLE II

Minimum Concentration per ml of antibiotic required to inhibit the Standard Staphylococcus

Penicillin	Streptomycin	Chloromycetin	Aureomycin	Terramycin
0.03 units (0.02 µg)	0.5 µg	1.5 µg	0.25 µg	0.25 µg

The staphylococcus was grown on nutrient agar and before use was subcultured in nutrient broth at 37° C for eighteen–twenty hours. This culture was diluted five times, and the average number of cells per ml was then about 100 million by opacity standards.

Preparation of the Standard Graphs —The preparation of the standard graph for penicillin will be described in detail. Graphs for the other antibiotics are prepared in a similar manner and do not require description.

Solutions of penicillin in distilled water were prepared to give the following range of concentrations per disc —0.001, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0 and 10 units. The discs were impregnated as previously described. Petri dishes containing nutrient agar or blood agar were surface-sown with the standard staphylococcus. The nutrient broth culture containing 100 million organisms per ml was flooded on to the surface of the plates with a capillary pipette, the plate tilted and the excess pipetted off. The plates were then inverted and dried in the incubator for half an hour at 37° C.

Ten blood agar plates were taken for each concentration of disc, that was, a total of 100 plates, and a minimum of ten estimations for each concentration were carried out. The discs may be applied to the centre of the surface or eccentrically, in which case more than one disc can be placed on each plate.

Each disc was applied carefully to the surface of the agar without lateral movement once the surface had been touched. Where necessary they were flattened down with the points of the forceps.

The plates were then incubated for eighteen–twenty hours at 37° C; the resulting zones of inhibition were measured and plotted on graph-paper.

Zones of inhibition—As often described with sensitive organisms, there are several well-defined zones apparent from within outwards around a source of antibiotic on inoculated solid media

- They are (Fig 1) (a) complete inhibition of growth,
 (b) delayed growth,
 (c) lysis, where the shadows of bacterial colonies are present,
 (d) stimulation of growth, and
 (e) normal growth

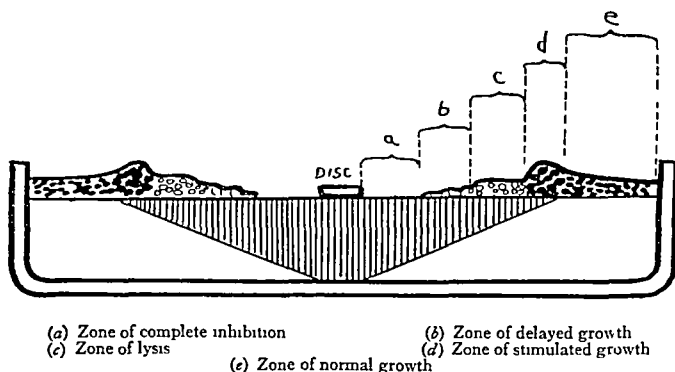


FIG 1—Petri dish in section showing in diagrammatic form the theoretical concentration gradient of antibiotic after diffusion from the disc. Also diagrammatically represented are the various zones of inhibition and growth that may occur

One or more of these zones may not be apparent, depending upon the antibiotic, the sensitivity of the organism and the time of incubation. Measurement is best carried out with dividers in a strong reflected light, and we found it most satisfactory to include the zone of lysis, when present, in our measurements. The diameter of the zone of inhibition is taken in preference to the radius or the distance from the margin of the disc. The results given in Table III are typical of the readings obtained in many experiments.

TABLE III
Zones of Inhibition with Different Concentrations of Penicillin per Disc

Concentration of Penicillin per Disc (units)	Zone of Inhibition (m m)
0.001	0
0.005	0
0.01	7.0
0.05	12.8
0.1	19.6
0.2	22.7
0.5	25.5
1.0	30.5
2.0	33.0
5.0	35.1
10.0	38.8

The graph is constructed by plotting the zone of inhibition in mm, against the logarithm of the concentration in microgrammes or units. Over a wide range of concentration the result is a straight line. Specimen graphs for penicillin and the other antibiotics are given in Figs 2-6

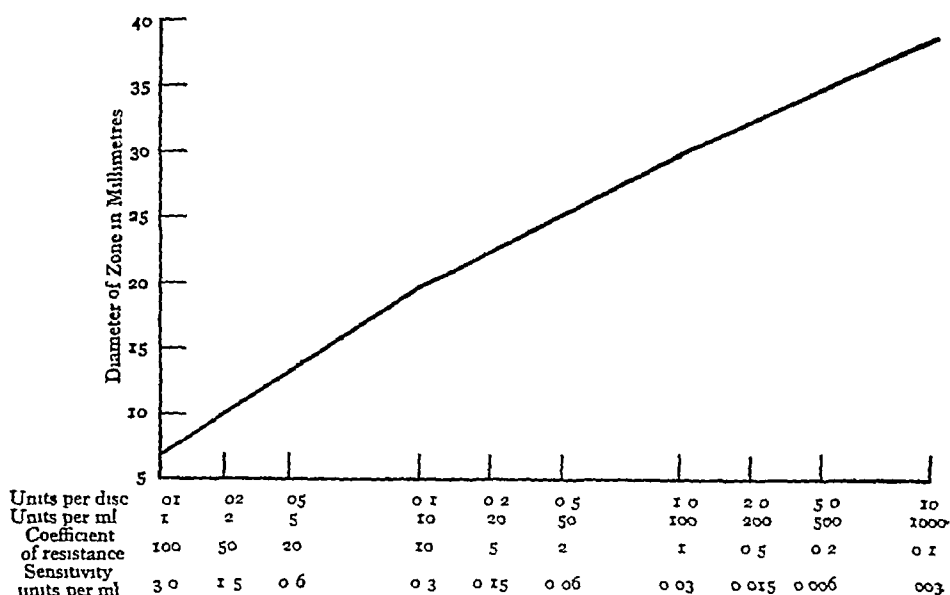


FIG 2 —Standard Graph for Penicillin

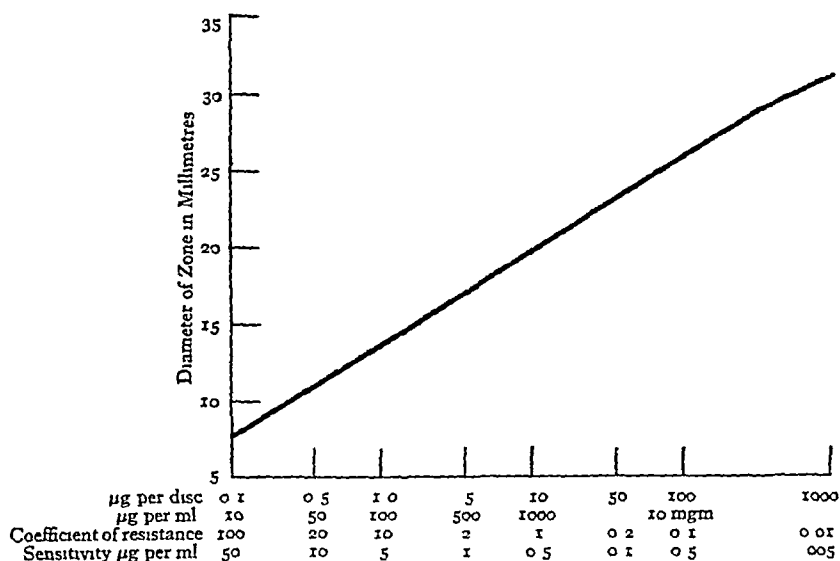


FIG 3 —Standard Graph for Streptomycin

It should be noted that the smallest zone of inhibition that can be measured is that which is just visibly greater than the disc, about 7.0 mm in diameter

As can be visualised from Fig 1 the concentration of the antibiotic constantly decreases with distance from the disc. Some antibiotics

Note —Those wishing to follow the detailed technique described in Figs 1 to 6 should transcribe and enlarge the graphs on sectional paper

diffuse more rapidly than others. If the organism is inoculated before applying the disc to the medium, diffusion must take place rapidly enough to produce clear-cut zones of inhibition. If conditions are identical in repeated tests, the rate and extent of diffusion will remain constant, and identical zones of inhibition will be obtained.

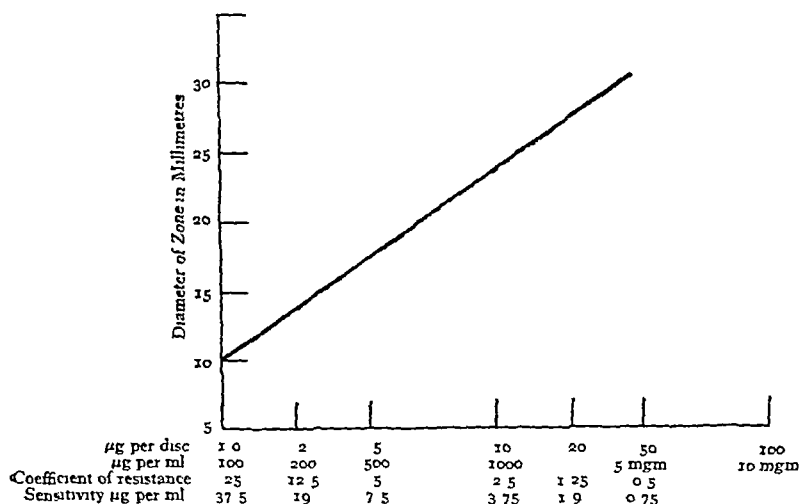


FIG 4—Standard Graph for Chloromycetin

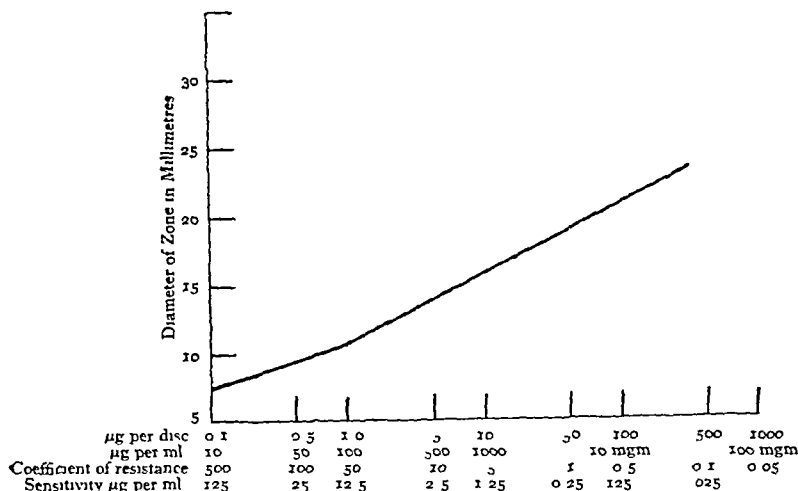


FIG 5—Standard Graph for Aureomycin

Absolutely constant conditions are impractical in routine work, we have investigated the variable factors to determine their effect on the results and to decide upon the latitude which may be allowed without significant alteration in the zones of inhibition. As a result of these experiments we have been able to adopt certain standards and procedures which constitute our modifications of the original method.

EXPERIMENT 1 *Variation in the Size of Disc*—Different sizes of disc were prepared of diameter ranging from 4 to 12 mm. Using 1.0 ml

of fluid the larger discs are not uniformly saturated as 100 will absorb more than this amount. The smaller discs are uniformly saturated but do not absorb all the fluid. The results obtained over a number of experiments with discs of different sizes is shown in Table IV. The

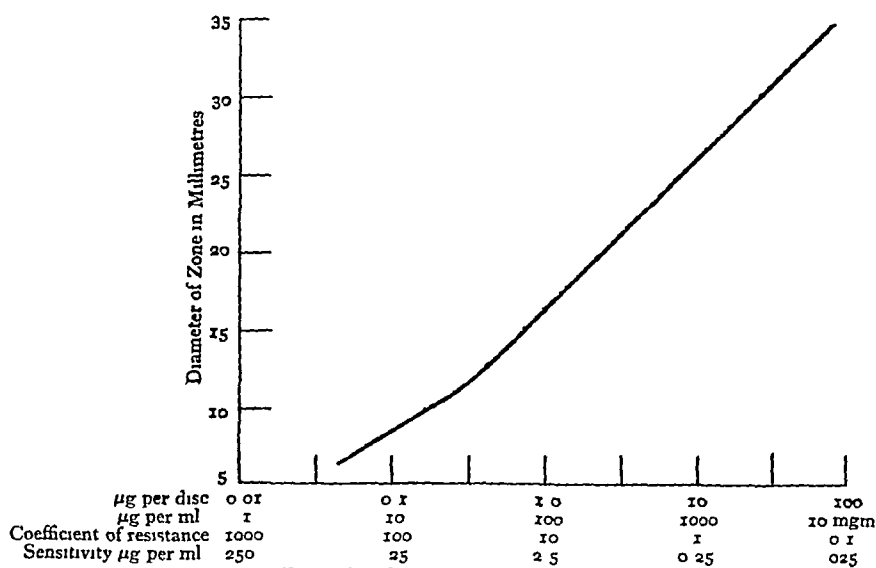


FIG. 6—Standard Graph for Terramycin

size of disc, 100 of which will absorb 10 ml of fluid, is about 7.0 mm. The disc of 6.8 mm, being slightly smaller, ensures that each disc is fully saturated when 100 are mixed with 10 ml of solution and the reduction of antibiotic content is insignificant. For this reason the 6.8 mm disc was adopted as our standard.

EXPERIMENT 2 *Variation in Type of Paper*—6.8 mm discs of Whatman No. 1, No. 2 and No. 40 and of thick and thin blotting paper were used under conditions similar to those in Experiment 1. There

TABLE IV

Zones of Inhibition with Different Sizes of Disc

Size of Disc	Number of Tests	100 Discs to 10 ml Solution (zones in mm)	Discs Individually Saturated (zones in mm)
12.0	50	35	34
8.0	50	33	32
6.8	50	30	30
5.0	50	27	27

was little variation between the zones obtained with the filter papers but the blotting paper gave unsatisfactory results since a disc of this size absorbs more than 0.01 ml. The results then depend upon the amount of fluid that the paper is capable of absorbing.

EXPERIMENT 3 *Conditions of Storage*—Discs prepared in the way already described were stored under different conditions and then tested for potency as shown by the zones of inhibition. As can be seen from Table V the discs retained their potency for a longer period in the

refrigerator than at room temperature, and longer when wet than when dry. The variation in zone diameter was also less when wet than when dry.

Discs saturated with aqueous solutions of the other antibiotics were

TABLE V
The Effect of Storage and Time on Potency of Discs

Penicillin 1 Unit Disc		Time (Zones of inhibition in mm)				
		1 Week	4 Weeks	2 Months	3 Months	4 Months
Wet	Room temperature	30	29	29	28	28
	4° C	30	30	30	30	29
Dry	Room temperature	29	29	28	27	26
	4° C	29	28	27	27	27

TABLE VI
Showing the Effect of Time on the Potency of Discs

Antibiotic µg / Disc	Time in Months (Zones of inhibition in mm)									
	1	2	3	4	5	6	9	12	18	24
Streptomycin 10	18	18	18	18	18	18	17	17	16	15
Chloromycetin 25	30	30	30	30	30	30	27	25		
Aureomycin 50	21	21	20	20	20	18				
Terramycin 10	27	26	23	23						

TABLE VII
Effect of the Amount Inoculum on Zone of Inhibition

Inoculum (orgs / ml)	Penicillin Discs Containing 10 Units		
	Number of Tests	Zone of Inhibition in mm	Remarks
50,000	50	37.5	Individual colonies on plate
500,000	50	30.5	Almost confluent growth
5,000,000	50	30.5	Confluent growth
50,000,000	50	30.0	Confluent growth
100,000,000	50	30.5	Confluent growth
200,000,000	25	30.0	Confluent growth
500,000,000	25	29.0	Confluent growth
1,000,000,000	10	28.5	Confluent growth

stored in the wet state and tested for potency after lengthening periods of time. The results are given in Table VI.

EXPERIMENT 4 *Amount of the Inoculum*—In the standard procedure already described the culture plates are seeded with broth containing approximately 100 million staphylococcal cells per mm. The effect of varying this inoculum was tried and as will be seen from Table VII, within fairly broad limits, there is no great variation in the zones of inhibition produced by discs of the same potency.

That this does not hold true for all antibiotics, particularly Terramycin, is shown in Table VIII where the effect of a ten-fold variation in inoculum is shown for each agent

EXPERIMENT 5 *Age of the Inoculum*—The older the culture, the smaller the number of viable cells it will contain, the lag period for

TABLE VIII
The Effect of Inoculum on Zones of Inhibition

Antibiotic	Inoculum (cells/ml)	Zone of Inhibition (mm)
Streptomycin	20,000,000	18
	200,000,000	17
Chloromycetin	20,000,000	30
	200,000,000	28
Aureomycin	20,000,000	21
	200,000,000	18
Terramycin	20,000,000	27
	200,000,000	21

these cells will be longer than for those used in the logarithmic period of growth, as in experiment 4. However, in practice the age of the cells of the inoculum has an insignificant effect on the zone diameter

EXPERIMENT 6 *Variation in the Method of Inoculation*—Pour plates of nutrient agar previously seeded with the staphylococcus are not recommended because the zones of inhibition are more difficult to read and their preparation is more complicated. Surface seeding gives the best results when the distribution of the organisms is reasonably

TABLE IX
Showing Effect of Different Methods of Inoculation Plates

Method of Inoculation	Inoculum (orgs/ml)	Zone of Inhibition (mm)
Pour plates	100,000,000	28
Fixed volume of inoculum	100,000,000	30
Flooded plate	100,000,000	30

uniform. A small amount of broth culture may be spread over the surface of the medium with a suitable instrument and allowed to dry, if carefully done this results in a uniform growth. However it is easier to pour an excess of the diluted broth over the surface of the medium, drain off the excess, and dry in the incubator.

The zones of inhibition obtained by these methods are similar (Table IX)

The time of drying the plates in the incubator at 37° C does not

affect the zones of inhibition provided that it does not exceed two hours. After two hours the plates become dehydrated to some extent and colony growth begins, both factors influence test readings.

EXPERIMENT 7 *Type of Medium Used*—The pH of the medium has been shown to have a marked effect on the zones of inhibition of growth of penicillin (Schmidt, 1944), streptomycin (Loo, 1944) and aureomycin (Pratt and Duffrenoy, 1948, and Ingram, 1950). We did not pursue this as, with few exceptions, the routine laboratory media have a pH around 7.2-7.6. Variation within these limits has insignificant effect upon the zones obtained with any of the antibiotics.

The agar base of the medium must be homogeneous, otherwise there will be irregularities in diffusion.

The effect of the concentration of agar, and the addition of other materials such as blood (blood agar medium) and bile-salts (McConkey's

TABLE X

Showing the Effect of Concentration of Agar and of Other Ingredients in the Medium

Concentration of Agar	Medium	Zones of Inhibition in mm				
		Penicillin	Strepto- mycin	Chloro- mycetin	Aureomycin	Terramycin
1 per cent.	Nutrient agar	29	18	30	20	26
2 "	"	30	19	29	20	25
3 "	"	30	19	29	18	25
4 "	"	29	18	29	18	25
6 "	"	23	16	25	16	24
2 "	Blood agar	30	19	30	19	24
2 "	McConkey	30	20	30	19	24

medium) were investigated. The more concentrated agar (Table X) retards diffusion of penicillin since the zones of inhibition are smaller but there is no significant difference within the range of concentrations usually used in preparing laboratory media (1.5-3.0 per cent). The zones of inhibition obtained on blood agar medium and on McConkey's medium are the same as those obtained on nutrient agar medium.

EXPERIMENT 8 *Thickness of the Medium*—Other conditions being equal, it is the depth of the medium which determines the extent of diffusion of the antibiotic (De Beer and Sherwood, 1944), the thicker the agar medium the smaller the zone of inhibition. When the medium is very thin there is the additional factor of indistinct margins to the zones of inhibition, making exact measurement difficult. Using the plates poured daily for routine use in the laboratory, we found no significant variation on this account.

We use 7 cm. Petri dishes for routine work and find 5 ml. of medium satisfactory. Table XI shows the zones of inhibition obtained with thicker and thinner layers of medium.

EXPERIMENT 9 *Time of Incubation*—Penicillin and the other antibiotics diffuse rapidly outwards before any appreciable growth has taken place. We may thus disregard the effect of time on the diffusion of the active substance.

The standard organism grows appreciably in six-eight hours' time, and by then there are well-marked zones of inhibition of growth with penicillin. These are zones of absolute inhibition and correspond in size to the zone of absolute inhibition seen after twenty hours. The zone of lysis forms between ten-twenty hours and is included by us in the zone measured. However, there is no reason why the zone of absolute inhibition should not be used as the criterion and read at eight hours if desired, this is usually inconvenient unless the plates are inoculated first thing in the morning. Further, it will not be feasible

TABLE XI
Showing the Effect of the Thickness of the Medium

Size of Plate Diameter in cm	Amount of Medium per Plate	Thickness of Medium	Zones in mm				
			Penicillin	Streptomycin	Chloromycetin	Aureomycin	Terramycin
7	30 ml	0.8 mm	33				
7	50 "	1.3 "	30	20	29	18	27
7	75 "	2.0 "	28				
7	100 "	2.6 "	26	20	27	17	25
7	150 "	4.0 "	22				

in the sensitivity determination of a slow-growing organism. The zone of lysis does extend after twenty hours and is appreciably larger at forty-eight hours, for this reason readings should not be too long delayed.

EXPERIMENT 10 *Incubator Temperature*—Variation within the usual range of incubator temperatures used in the laboratory produces little effect upon the zone of inhibition provided that growth actually takes place.

SUMMARY OF EXPERIMENTS 1-10

As a result of these experiments the following points are of importance in obtaining consistent results.

Petri-dishes containing a uniform thickness of medium are used. They are surface-sown with an over-night broth culture of the standard organism for assay purposes, or with the test organism, for sensitivity determination. The plates are then dried for thirty minutes at 37° C, the discs are then applied. It is essential that the discs be of uniform size and material, and similar to those used in the preparation of the standard graphs. Measurements are made after eighteen-twenty hours' incubation.

Adequate results can be obtained with routine laboratory plates sown in a variety of ways, these are described below.

EXPERIMENT 11 *Test of the Reproducibility of Results*—1000 penicillin 1 unit discs were taken from freshly prepared stock and used under the conditions just described Table XII gives the results

THE DETERMINATION OF THE SENSITIVITY OF AN ORGANISM

The exact identity of the organisms present is unnecessary for sensitivity determinations as long as the colonies are individually recognisable on the medium

An initial sensitivity result can be obtained from the primary cultures by placing discs on suitably inoculated plates at the time of inoculation. The variety of media inoculated, and atmospheres of incubation, must be sufficiently wide to ensure growth of any species of micro-organism likely to be present For example, discs must be placed on anærobic blood medium if anærobic streptococci are anticipated This test may be regarded as a screening test

The Screen Test—This may be varied to suit different conditions.

TABLE XII

Results of 1000 Consecutive Tests with 1 Unit Penicillin Discs

Number of Tests	Mean of Zones mm	Standard Deviation	Standard Error of Mean
1000	30.13	1.075	0.034

(1) Where the sensitivity to one antibiotic only is required (a) Area of initial inoculation in primary cultures of the specimen is made larger than usual so that it covers about one-third of a 3½ ins Petri-dish and is spread as uniformly as possible The disc containing the antibiotic is applied to the centre of the area After incubation the zone of inhibition of growth is measured and in most cases will give a satisfactory assessment when compared with the more detailed test carried out at a later stage

There will be a number of tests where the result cannot be assessed properly as (i) where more than one species are present, the growth of an insensitive organism occasionally masks the sensitivity of a sensitive organism, and (ii) where the inoculum is so sparse that a satisfactory zone of inhibition is not formed (b) Alternatively, a plate may be inoculated especially for the discs by stroking out the material with a loop or swab across the whole area of the plate as uniformly as possible

(2) Where the sensitivity to more than one antibiotic is required

A large Petri-dish or several smaller dishes should be inoculated as described in (1) (b) and the individual discs applied at suitably spaced intervals A 4 in Petri-dish will accommodate five discs comfortably

Method of Reading Results—The diameter of the zone produced by the disc on the plate cultures of the organism is measured in mm.

From the standard graph prepared for the particular antibiotic, the concentration of the antibiotic to which the organism is sensitive, can be read off directly in figures together with its coefficient-of-resistance compared with the standard Oxford Staphylococcus

The initial screening test will give information usually adequate for clinical purposes and no further sensitivity determination will be necessary. However, it is often desirable to carry out further tests in order to obtain a more exact estimation or to determine the sensitivity to additional antibiotic substances. In such cases we carry out the sensitivity determination on subcultures of the test organism with a standardised inoculum.

The Sensitivity Test on Subcultures of the Test Organism—This can be carried out as soon as the organisms have been isolated. Subcultures are made in a suitable fluid medium and are usually incubated for eighteen hours, but often for less. The resulting cultures are diluted to give approximately 100 million cells per ml by opacity standards, and the test plates are surface seeded. One plate is sufficient for each organism to be tested, but as many as desired may be inoculated as duplicates. The disc for each antibiotic is then applied and the zones of inhibition growth read after eighteen-twenty hours' incubation.

The sensitivity may be read off from the standard curve as before.

In a case where the result of a sensitivity test is urgently required and it has not been feasible to carry out the screening test, for example with a blood culture, a heated blood agar plate may be seeded with material from the primary culture in the usual way and the required disc applied. After six-ten hours the zone can be measured if the organism has grown sufficiently. This zone will differ from the zone that would be obtained after eighteen-twenty hours, and due allowance must be made in interpreting the sensitivity values.

THE REPORTING OF RESULTS

Only in special cases such as septicæmia and in research work is it necessary to know the exact level of sensitivity expressed in microgrammes per ml, units or coefficient of resistance. An opinion expressed in terms such as "sensitive," "relatively resistant" and "resistant," should suffice for clinical purposes.

Since *in vivo* sensitivities cannot be accurately gauged from *in vitro* levels of sensitivity, mathematical expressions of these might even be misleading. We therefore use descriptive words, but relate them to two arbitrary ranges of *in vitro* concentrations, one range (Table XIV) is used in reporting examinations of the urine, and the second (Table XIII) is used for all other specimens, it is based on the average systemic levels of the antibiotics usually obtained during treatment.

In determining these ranges we have attempted to combine the experience of our clinical colleagues in Edinburgh with our reviews of follow-up bacteriological examinations.

THE PRESENCE AND DETECTION OF RESISTANT COLONIES

Occasionally within the clear zone of inhibition, a few colonies may grow more or less right up to the disc. If these colonies are of the same species then they may be regarded as resistant variants. Alternatively they may be another species separated by the selective activity of the antibiotic.

The resistant colonies may be subcultured and the actual sensitivity

TABLE XIII

Correlation of Clinical Terms with Sensitivity Values for Usual Systemic Concentrations

Term for Clinical Use		Antibiotic In vitro Levels in $\mu\text{g/ml}$				
		Penicillin	Streptomycin	Chloramphenicol	Aureomycin	Tetracycline
SENSITIVE	Up to	0.3	1.0	2.5	2.5	1.0
RELATIVELY RESISTANT	Up to	1.0	10.0	10.0	10.0	5.0
RESISTANT	Greater than	1.0	10.0	10.0	10.0	5.0

TABLE XIV

Correlation of Clinical Terms with the Sensitivity Values for Usual Urinary Concentrations

Term for Clinical Use		Antibiotic In vitro Levels in $\mu\text{g/ml}$				
		Penicillin	Streptomycin	Chloramphenicol	Aureomycin	Tetracycline
SENSITIVE	Up to	50	10	10	15	10
RELATIVELY RESISTANT	Up to	100	100	40	100	25
RESISTANT	Greater than	200	100	40	100	25

determined. Their presence will usually weigh heavily against the use of that particular antibiotic.

A heavy inoculum of 1000 million organisms, or more per ml may be used to seed the test plates where it is desired to determine the presence or absence of resistant variants in a culture. This is especially applicable to urinary tract pathogens. The heavier the inoculum, the greater the chance of isolating resistant variants. The practical use of this has already been shown in the case of Myco tuberculosis by Tinne (1950).

PROCEDURE WITH ANTIBIOTICS OTHER THAN PENICILLIN

As we already said the procedure given is the same for

antibiotics in common use at present Streptomycin and chloromycetin behave exactly like penicillin with regard to these tests, further discussion may therefore be confined to aureomycin and terramycin

(1) *Aureomycin*—This antibiotic is susceptible to certain substances present in blood, and sometimes in peptones, used to make media (Herrell, 1950, Bliss and Chandler, 1948) so that it tends to be inactivated during the period of growth of the test organism This is one of the chief reasons for the relatively small zones of inhibition with aureomycin and the tendency for the test organism to grow inwards towards the disc during the later hours of incubation We can overcome this in three ways

(a) By using medium with a pH of 5.5 (buffered) when the inactivating substances are rendered inert and the zones of inhibition are much larger and better defined Unfortunately many bacteria to be tested will not grow at this pH level and also we must admit that conditions will be even further removed from those likely to be present *in vivo*

(b) By adopting the policy, already referred to, of reading the zones of inhibition after eight hours' incubation

(c) By incorporating reducing substances in the medium or incubating under anærobic conditions (Price, Randall and Welsh, 1948)

(2) *Terramycin*—The zones of inhibition around a terramycin disc are clear cut in the early hours of incubation and we have adopted the technique of reading results after eight-ten hours' incubation

There is a great difference between the bacteriostatic and bactericidal concentrations of terramycin for most organisms, this would appear to be the reason for the diminished zone of inhibition during the later hours of incubation This of course means that in accepting the eight-hour zones we are taking the "bacteriostatic" level, the "bactericidal" level is related to the usually much smaller zone obtained after longer incubation This reasoning is substantiated by parallel serial dilution tube tests where the wide gap between bacteriostatic and bactericidal levels is obvious

THE DETERMINATION OF THE SENSITIVITY TO STREPTOMYCIN OF MYCO TUBERCULOSIS

The determination of the sensitivity of *M. tuberculosis* to antibiotics presents difficulties—among others, the particularly slow rate of growth of the organism in culture

We have found that it is possible to use the disc diffusion technique for the sensitivity determination of this organism to streptomycin So far we have carried out only a limited number of tests and are attempting to improve the technique, we mention this merely to indicate that satisfactory zones of inhibition can be obtained

Lowenstein-Jensen, or similar medium, is coagulated in Petri-

dishes so that the thickness of the medium is similar to that used for the routine sensitivity tests. Material containing the tubercle bacillus (this may be a concentrate of sputum, etc., known to contain the bacillus, or an emulsion of a culture of the organism) is spread over the surface of the medium as uniformly as possible, and allowed to dry. The discs of streptomycin (10 μg /disc) and Para-amino salicylic (200 μg /disc) are then applied to the surface of the medium. The space between the lid and the base of the Petri-dish is sealed with vaseline-paraffin wax mixture to prevent dessication, and the plates are incubated for the time required to produce visible growth. Aeration of the cultures is carried out at the usual intervals.

Using the standard H 37 Rv strain of *M. tuberculosis* (kindly supplied by Professor C. P. Beattie) the zones of inhibition obtained with the streptomycin disc correspond fairly well with the calculated zone for an organism sensitive to 0.5 μg /ml of streptomycin.

Satisfactory zones are frequently obtained within ten days, and as this is possible with primary cultures of sputa, the method may have some practical application.

THE OBSERVATION OF THE PRESENCE OR ABSENCE OF SYNERGISTIC INHIBITORY EFFECT BY COMBINATIONS OF ANTIBIOTICS

The combination of two or more antibiotics is being more widely used in treatment with or without definite evidence that the pathogens are more sensitive to the combination than to one or other of the components of the mixture, alone. The effect of such a combination on bacteria can be shown when antibiotics are mixed in fluid media but has been more difficult to demonstrate with solid media using diffusion techniques. Placing a disc of antibiotic A on top of a disc of antibiotic B, or *vice versa* may not be very satisfactory as A may diffuse more rapidly and to a greater extent than B, so that all the inhibitory effect is due to A, B being present in effective concentration only within the zone of inhibition due to A.

To forecast the synergistic effect of combinations of antibiotics we use the disc-diffusion method after the manner of Lamanna and Shapiro (1943). The sensitivity of the test organism to antibiotics A and B of the intended combination is determined in the usual way. Next, a fresh culture plate is sown with the test organism, and discs of A and B are applied at a distance "X" mm apart, where X equals $a + b$, a being the radius of the zone of inhibition to antibiotic A, and b the radius of the zone to B. After incubation the two zones of inhibition will just make contact and there will be a thin wedge of growth on either side of the point of contact of the zones. When there is appreciable additive or synergistic inhibitory effect (Kolmer, 1945) of individually sub-inhibitory concentrations of antibiotics A and B, the growth in the area of the wedges will be inhibited and can be seen without difficulty.

So far we have not attempted to interpret this in a quantitative manner

Mutual interference of antibiotics may also be demonstrated by this method

COMPARISON OF THE DISC DIFFUSION METHOD WITH OTHER DIFFUSION METHODS AND THE SERIAL DILUTION TUBE METHOD

The "ditch" (Fleming, 1929) and "cylinder" (Foster and Woodruff, 1943, Abraham, 1941, Foster and Woodruff, 1944) plate techniques give results comparable with the disc modification but they are infinitely more tedious, less accurate and give less easily reproducible results

The serial dilution tube method is very much more laborious than the disc-diffusion method. In routine work mistakes tend to occur more easily with this method, pipetting errors being especially common. The medium must adequately support the growth of the test organism otherwise very discrepant results may be obtained. When the disc-diffusion method was carried out in parallel with the serial dilution tube method, closely similar results were obtained.

In one experiment, 100 consecutive cases of staphylococcal infection were taken and the sensitivity of the infecting organism determined by the screen test we have described for primary cultures, after subculture the sensitivity was again determined, both by the serial dilution tube method and by the diffusion method. There was satisfactory correlation between the results of the screen test and those of the serial dilution tube test, and even closer agreement between the tests on subculture. 95 of the 100 cases gave sensitivity results which agreed in all three tests. Of the remaining 5 cases, 3 gave results in the screen test which placed them in the "relatively resistant" zone of the penicillin graph, on subculture they proved to be fully resistant to 20 units by both the serial dilution tube method and by the disc method. A fourth organism was "sensitive" by the screen test, and sensitive to 10 unit/ml by the tests on subculture. In the fifth case the organism, sensitive to 0.2 units by the screen test and diffusion test on subculture, was found to be resistant to 20 units by the serial dilution tube method.

This experiment is typical of our experience and shows that the diffusion technique is as accurate as the more complicated tube test for all purposes. In addition it has the advantage of simplicity, speed and easy reproductibility.

THE ASSAY OF ANTIBIOTIC SUBSTANCES

The number of requests to assay antibiotics in body fluids is small in a routing hospital laboratory.

Paper discs may be used to assay these substances and, within the limitations of the method, provides a very simple and rapid procedure. The chief limitation is in the amount of antibiotic that can be detected.

This corresponds to the smallest amount which will give an appreciable zone of inhibition around the disc, as the disc will only absorb 0.01 ml, the amount of antibiotic present in 1.0 ml of the test fluid must be considerable. The practical lower limits assayable for each antibiotic with the standard staphylococcus are as follows —

TABLE XV
Assayable Lower Limits ug/ml

Penicillin	Streptomycin	Chloromycetin	Aureomycin	Terramycin
2.0	15.0	75.0	10.0	10.0

The sensitivity of the test may be increased by layering discs, one on top of the other, up to a maximum of 4, and this has been found to give fairly satisfactory results. In this manner concentrations of penicillin of 0.5 units per ml may be assayed.

The range of the test may also be increased by using a particularly sensitive organism for each antibiotic. This necessitates the construction of separate standard curves, and will not be considered here.

In our opinion the disc method is of value in assaying specimens of urine and other fluids where the concentration expected is high, it is also useful for checking assays on laboratory standard solutions of antibiotics.

The Method of Assay — The technique is the same as that described for determinations of the sensitivity of an organism except that the unknown quantity is the amount of antibiotic in the disc.

The standard staphylococcus in eighteen-hour broth culture, 100 million cells per ml, is surface seeded on nutrient agar plates which are then dried for thirty minutes. One ml of the fluid for assay may be added to 100 sterile discs in a bottle, or alternatively, individual discs may be soaked with the fluid by dipping. The latter method is not quite so accurate but is more economical in discs. Care must be taken not to carry over an excess of fluid, and this is best avoided by draining the disc against the side of the container.

The zones are read after eighteen–twenty hours, the concentration per disc or ml can be read off from the standard curve for the particular antibiotic concerned.

DISCUSSION

Clinical diagnosis is not a dependable guide to the microbial flora present and certainly not to their antibiotic sensitivity. Bacteriological data not only serve as guides to the drug of choice, and alternatives, but also as an indication of the adequate dose.

Clinicians agree in principle that in most bacterial infections the sensitivity of the causative organism should be determined before chemotherapy is begun, but inadequate laboratory resources, incon-

veniently situated laboratories or delay in the receipt of laboratory advice make this difficult or often impossible. Since progress has been made in the development of rapid laboratory techniques for the purpose, and the range of available antibiotics is still expanding—each with its own antimicrobial “spectrum”—it can be categorically stated that specimens should now be taken for bacteriological examination before these remedies are exhibited and that it is advisable to know the pre-treatment sensitivity of the causative organism. Of course this may be impossible if no material containing the causative organism is available, or if, as in an emergency, it is necessary to give an antibiotic before the result of laboratory data is to hand.

The premature use of antibiotics for the alleviation of symptoms, *e.g.* pain or fever, or as an aid to diagnosis is to be deprecated. This practice masks symptoms, delays effective treatment, and complicates laboratory identification of the causative organism, the bacteria assume bizarre characters and growth may be temporarily reduced.

A working knowledge of the anti-microbial “spectrum” possessed by each of the five antibiotics in general use, is of advantage, but this has been perhaps over emphasised by those concerned in the production and distribution of these drugs. It should be remembered that all organisms of a particular group or species are alike in their sensitivity to one particular antibiotic, to give only a few examples, the antibiotic of choice for coagulase-positive staphylococci, streptococci other than those of Lancefield’s Group A, and Gram-negative bacilli of wounds and of the urinary tract, can only be determined by a sensitivity test in each individual case.

In practice there is no reliable guide to the therapeutic use of antibiotics other than *in vitro* sensitivity allied to clinical experience. There are individual cases in which the taking of a pre-treatment specimen for bacteriological examination is inexpedient—there are others such as meningococcal meningitis in which the exhibition of a sulphonamide should not be delayed for sensitivity determination—but in general the choice and dose of antibiotic should be guided by the bacteriological findings in each individual case.

The object of the work presented in this paper has been the adaptation of tests in connection with antibiotics to routine bacteriological procedures in a hospital laboratory.

When the laboratory and clinical points of view are correlated there is no doubt that diffusion methods with solid media are the methods of choice, they show more clearly than other test methods the different ways in which an organism may react to antibiotics *in vitro*.

Of the diffusion methods, the impregnated disc technique is the most simple and flexible. We have adapted the technique to cover all antibiotic work likely to be required of a hospital laboratory and we have found the results adequate for practical purposes.

In most laboratories the staff engaged in preparing and setting primary cultures could undertake the screen test on every spec

sent for bacteriological examination—without excessive increase in the amount of work when the tests become routine. Subculture sensitivity tests are a different matter, but one worker can undertake more than 100 in a day if necessary, and the difference in time required to apply the separate discs for each additional antibiotic is small compared with the time taken in preparing and seeding the plates.

It is suggested that sensitivity levels be reported in the form of descriptive words correlated with levels known to exist in body fluids when the patient is under treatment. Owing to the higher levels of various antibiotics in the urine as compared with the concentration obtainable in the blood and tissue fluids, we use two scales for the interpretation of *in vitro* levels.

It is as well to remember that we are as yet at an elementary stage in correlating the clinical administration of antibiotics with *in vitro* sensitivity determinations designed to give some idea of the amount of antibiotic required.

It is possible that the sensitivity determination, using the primary culture, gives a result which is actually more nearly related to *in vivo* conditions, especially when multiple species of organisms are concerned. The mutual effect of the organisms on one another is coupled with the action of the antibiotic, so the test result may well differ from that obtained when the organisms are tested in pure subcultures.

If the discs are applied to primary culture plates, apparent anomalies may occasionally influence the reading of the result, the inhibition by a given antibiotic may differ under aerobic and anaerobic conditions. It may be that the organism *in vivo* is subject to a reduced oxidation-reduction potential, in such a case the anaerobic sensitivity level would perhaps have greater significance. As it is not possible to decide the actual conditions in the patient, it is our custom to report the lower level of sensitivity, where there is any clinical reason for so doing.

We believe that the study of the zone of inhibition surrounding the source of an antibiotic on a Petri-dish, can give a great deal of information about the action of the antibiotic on the organism under test, and that this information may be applicable to clinical work. The appearance of a few resistant colonies within the zone of inhibition of the majority is of significance. The merging of zones between two antibiotics is an indication of additive or synergistic inhibition. The difference between the bactericidal and bacteriostatic effects of an antibiotic can be very clearly seen and would appear to have great significance with agents such as terramycin. Using the serial dilution tube technique, visual end-points give sensitivity values which are lower than the bactericidal level determined by the recovery of viable cells from the apparently clear tubes. This can be seen on diffusion plates where the well-marked zone of inhibition, present during the early hours of incubation, is encroached upon during the later hours. Within the bactericidal concentration for the test organism, all cells on the surface of the medium are killed and at no time will there be

growth in the zone, no matter how long the plate is incubated. This zone of complete inhibition corresponds to the bactericidal level. Outside the zone of complete inhibition the concentration falls to the bacteriostatic level and within the zone, corresponding to this second concentration, the cells on the surface of the medium are not killed; the lag period of growth is increased. Once this lag period is over, growth is demonstrated by a fine haze over the surface of the medium spreading inwards to the periphery of the zone of complete inhibition. With terramycin this zone of delayed growth or bacteriostasis, is particularly large, varying of course with the particular organism concerned. Probably this has a distinct significance with regard to the outcome of treatment with this drug.

SUMMARY

Details are given whereby the disc method may be incorporated in the procedures of any hospital laboratory for all antibiotic work.

The methods described include a screening sensitivity test on primary plate cultures, a sensitivity test on subcultures, a method by which antibiotic synergism against any particular organism may be observed, and lastly, a method for the assay of antibiotics in fluid.

The few simple materials required are available in any hospital laboratory and no special culture media are necessary. No tedious controls are involved and dilutions of antibiotics need be made only once in three months.

As a screening test the method may be allied with the usual procedures involved in the isolation and identification of micro-organisms in hospital laboratories, the few additional manipulations are extremely simple and may be performed within a few seconds. The incorporation of the technique in routine bacteriological examinations actually facilitates the isolation of micro-organisms present in many specimens, the organisms and their sensitivity to the various antibiotics can generally be reported from primary cultures—that is to say, within twenty-four hours of the time the specimen is received.

By merely measuring the diameter of the zone of inhibition the sensitivity level and coefficient of resistance, compared with the standard staphylococcus, may be obtained from standard graphs. These are included in the text for terramycin, penicillin, streptomycin, chloromycetin and aureomycin, assays may be performed with equal facility.

Experiments performed to test accuracy show that this is adequate for clinical purposes. In other respects it has practical advantages over other techniques.

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STAPH AUREUS AIR INFECTION IN A MATERNITY HOSPITAL

By A T WALLACE, M D , D P H , and J P DUGUID, B Sc , M D
From the Bacteriology Department, University of Edinburgh

NEWBORN infants are especially susceptible to infection by *Staph. aureus*. Even the well-run maternity hospital often has a high incidence of infection among the babies during their week or so of residence. Pemphigus neonatorum, minor septic skin lesions, umbilical sepsis, nasal infection, blepharitis and conjunctivitis are common, and some cases occur of staphylococcal pneumonia, meningitis and osteomyelitis (Cass, 1940, Ludlam, 1947).

Investigations such as those of Elliot, Gilliespie and Holland (1941), Duncan and Walker (1942) and Allison and Hobbs (1947) have shown that a majority of infections may occur in outbreaks due to distinct serological types of *Staph aureus*. During the outbreak the epidemic strain is found in a multiplicity of sources in the hospital. It occurs in the lesions of clinically infected infants, and also in the noses of healthy carriers who include a large proportion of the well infants, mothers and nurses. *Staph aureus* contamination of the hands is likely to be present in as many as half of the nasal carriers. Commonly the milk of nursing mothers is infected, but this is not thought to be an important source of infection for the infants, it appears that the breast usually receives the infection from an already infected child (Duncan and Walker). The epidemic staphylococcus may be present and viable on the infant's garments and bedding, even after laundering, and in the floor dust and air of the hospital. In a few observations made with "settling plates," Elliot, Gilliespie and Holland (1941) and Allison and Hobbs (1947) found *Staph aureus* to be present in the air of the hospital nurseries during outbreaks of pemphigus. Allison and Hobbs regarded the degree of air infection as low, they concluded that the main reservoir of infection was the nasal passages of healthy carriers among the nursing staff, and that the main means of spread thence to the infants was probably by contact with the carrier's hands, in addition, infection from infant to infant by the commonly shared bath, towel and laundry was thought likely to play an important part.

The present investigation of *Staph aureus* infection in a maternity hospital unit was directed particularly to assessing the extent of infection of the air. For various reasons it was anticipated that airborne infection would prove to be of major importance. *Staph aureus* has been one of the pathogenic bacteria most commonly found in the air of occupied premises, for instance, in surgical operating theatres (Hart, 1937, 1938, Hart and Schiebel, 1939, Devenish and Miles, 1939, MacDonald, 1940), in surgical and burns wards (Miles *et al*, 1940, Bourdillon and Colebrook, 1946, Colebrook and Cawston,

1948), and in wards of an infants' hospital (Brooks, Wilson and Blackfan, 1942). In the case of other respiratory-tract bacteria which probably spread in the same way as *Staph aureus*, the practice of aseptic nursing procedures for avoidance of contact spread has generally failed to prevent a high incidence of cross-infections in open multi-bed wards, on the other hand, cross-infections have been eliminated where the patients were isolated in single-bed cells designed to prevent airborne spread (Allison and Brown, 1937, Wright, Shone and Tucker, 1941, Stalker, Whatley and Wright, 1942, Chapple, 1942).

CIRCUMSTANCES OF THE INVESTIGATION

The investigation was carried out during sixteen weeks from 12th March to 2nd July 1947, in the maternity unit of a large general hospital in Edinburgh. The unit consisted of several rooms opening into a common corridor, it included a mothers' ward (26×16×13 ft of nine beds), a large nursery (30×14×13 ft, of twenty-six cots), a small nursery (18×16×13 ft, of fourteen cots), a small washroom, a babies' changing room, an isolation ward and offices. The premises were clean and airy, the floors were of polished wood, the windows were large, of part-southerly exposure and usually kept open. There was no appearance of overcrowding. Most of the beds in the mothers' ward and over half of the cots in each nursery were occupied during the period of the investigation. The day and night nursing staffs together usually totalled twelve. The nurses wore masks and gowns when attending the babies. The babies were changed seven times a day or oftener, and were taken at four-hourly intervals to the mothers' ward for nursing. In the course of medical examinations, toilet, bed-making, serving meals and domestic cleaning, the ward and nurseries were entered frequently by doctors, nurses and ward maids, visitors were admitted only to the mothers' ward. Mother and child remained in hospital for about ten days.

During the spring of 1947 the maternity unit reported a high incidence of *Staph aureus* infections, this prevalence continued throughout the period of the investigation. Among the infants, septic skin lesions and conjunctivitis were especially common, and there was one fatal case of staphylococcal pneumonia. Among the mothers, there were cases of breast abscess, boils, conjunctivitis and Cæsarian wound infection due to *Staph aureus*. The taking of nasal swabs on one occasion revealed a high incidence of healthy carriers, 2 out of 7 nurses and 11 out of 26 babies carried *Staph aureus* in the nostrils.

EXPERIMENTAL METHODS

Two methods were used for examining the bacterial content of the air, namely, exposure of culture plates to direct sedimentation of infected particles ("settling plates"), and use of the slit sampler of Bourdillon, Lidwell and Thomas (1941). The "settling plates"

presented 10 sq in of culture medium surface, they were left open on a table in the centre of the room. The slit sampler was run at 1 cu ft per minute, with a slit-plate distance of 2 mm, it was placed centrally in the room at about 3 ft above the floor. No person was allowed to approach closely to the slit sampler, except the observer at the time of changing plates.

Four different culture media were used: (1) nutrient agar (1 per cent. meat extract, 1 per cent peptone, $\frac{1}{2}$ per cent sodium chloride and 2 per cent agar), (2) blood agar (nutrient agar with 5 per cent horse blood), (3) MacConkey agar (2 per cent peptone, $\frac{1}{2}$ per cent sodium taurocholate, 1 per cent lactose, 2 per cent agar and neutral red to tint), and (4) salt-milk agar (nutrient agar with 20 per cent milk and 7 per cent sodium chloride). The batch of MacConkey agar used gave good growth of *Staph aureus* with enhancement of pigmentation, and inhibited growth of many other airborne species. Similarly, the salt-milk agar was partially selective for *Staph aureus* because of its 7 per cent salt content (Chapman, 1945) and enhanced pigmentation because of its milk content (Christie and Keogh, 1940). Plates were incubated aerobically at 37°C for twenty-four hours and then left at room temperature for a further twenty-four hours. The colonies were counted with the aid of a plate microscope. All golden-coloured colonies which resembled *Staph aureus* were subcultured and tested for coagulase production, only the coagulase positive strains were recorded as *Staph aureus*.

TWENTY-FOUR HOURS SETTLING PLATE OBSERVATIONS

Observations with settling plates exposed for a continuous twenty-four-hour period were made on each of forty days chosen at intervals between 12th March and 2nd July, a MacConkey plate and a salt-milk agar plate were exposed in each room. *Staph aureus* was thereby recovered from the air of the maternity unit on thirty-six of the forty days, on twenty-six of forty days in the large nursery, on twenty-six of forty days in the small nursery, on eleven of fourteen days in the mothers' ward and on fourteen of twenty-three days in the washroom. The number of *Staph aureus* colonies obtained was small, seldom more than two or three per plate, the number did not vary much between the different rooms, nor between different weeks throughout the investigation.

SLIT SAMPLER AND SETTLING PLATE OBSERVATIONS DURING MORNINGS

On seven days during the investigation period, parallel observations with slit sampler and settling plates were made during the morning. In one of the nurseries, or in the mothers' ward, air sampling was carried out continuously from 7.30 a.m. till 2 p.m., the period of the day when the wards were busiest and the air infection presumably

highest MacConkey plates were used in the slit sampler on six occasions, and nutrient agar plates on the seventh, 25 cu ft of air was taken on to each plate in the slit sampler during the first twenty-five minutes of each successive half-hour throughout the morning. Concurrently, a blood-agar settling plate was exposed during each twenty-five-minute period. As a rough measure of the amount of activity in the ward during the taking of each sample, a record was made of the number of "entrances," that is the number of occasions on which a doctor, nurse or maid entered the ward.

The results of the seven experiments are summarised in Table I,

TABLE I

Air Contamination with Staph aureus and other Bacteria in a Maternity Hospital (Shows for each day the average number of bacteria carrying particles per cu ft of air taken by the slit sampler, and the average number recovered per 10 sq in settling plate per hour)

Date of experiment —	18/6	25/6	14/5	21/5	28/5	4/6	2/7	Overall Average
Room —	Large Nursery	Large Nursery	Small Nursery	Small Nursery	Mothers Ward	Mothers Ward	Mothers Ward	
Number of entrances	136	55		51	100	80	114	
Amount of ventilation —	Medium	Medium	Medium	Great	Very Great	Great	Medium	
Slit sampler * —								
Cubic ft. of air sampled	325	300	300	300	325	275	300	
All bacteria per cu ft	5.9	5.2	5.1	1.5	9.2	10.6	14.2	7.4
<i>Staph aureus</i> per cu ft	0.040	0.037	0.027	0.010	0.100	0.040	0.020	0.04
Settling plates † —								
Plate hours exposure	5½	4½		5	5	4½	5	
All bacteria per plate hour	43	30		21	110	87	132	71
<i>Staph aureus</i> per plate hour	0.9	0.2		0.2	1.0	0.24	0.2	0.46

* MacConkey agar plates except in experiment 2/7 when nutrient agar was used

† 10 sq in blood agar plates

and the detailed observations for one experiment in the large nursery are shown in Table II. In the seven days a total of 2125 cu ft of air was examined with the slit sampler, this was found to contain eighty-five particles carrying *Staph aureus*, an average of 0.04 per cu ft. Some *Staph aureus* were found present in the air in each room and on each day, the average numbers for the different days varied from 0.01 to 0.10 per cu ft. The results of the examinations with the settling plates were in general agreement with the slit sampler results, *Staph aureus* was recovered from the air on all of the seven days, the overall average recovery rate being 0.46 infected particles per 10 sq in plate per hour.

The amount of *Staph aureus* air contamination did not show obvious correlation either with the concurrent amount of activity as measured by the number of "entrances," or with the amount of ventilation as judged by the extent of window opening and the sensation of draught. The heaviest *Staph aureus* air contamination occurred on

the occasion when the ventilation was greatest namely, in the mothers' ward on 28th May, a breezy and sunny day when all windows were fully open and a strong draught was felt almost continuously

The *Staph aureus* colonies comprised 0.70 per cent of all colonies on the MacConkey plates exposed in the slit sampler (six experiments) and 0.68 per cent of all colonies on the blood-agar settling plates (six experiments)

DISCUSSION

Throughout sixteen weeks when infections were prevalent, *Staph aureus* was found to be present almost constantly in the air of the maternity ward and nurseries. The number of infected particles found

TABLE II

Air Contamination with Staph aureus and other Bacteria in Large Nursery during Morning of 18th June

Time	"Entrances"	Colonies per 25 cu. ft. of Air by Slit Sampler *		Colonies per 25 Minutes per 10 sq. in Settling Plate †	
		All Bacteria	<i>Staph aureus</i>	All Bacteria	<i>Staph aureus</i>
07 30 25	15	180	0	18	0
08 00 25	20	160	0	26	0
08 30 55	17	140	0	23	0
09 00 25	7	196	0	33	1
09 30 55	6	120	0	6	0
10 00 25	12	200	0	26	1
10 30 55	5	132	1	22	1
11 00 25	11	216	0	19	0
11 30 55	13	204	1	18	0
12 00 25	14	154	4	23	1
12 30 55	7	53	0	14	0
1 00 25	7	48	1	5	1
1 30 55	2	104	6	6	0

* MacConkey agar plates

† Blood agar plates

in the air was small. Nevertheless, because of the large volume of air respired, the amount of air infection observed was sufficient to ensure that each adult and baby would inhale *Staph aureus* on many occasions while in the hospital. The average morning air contamination was 0.04 *Staph aureus*-carrying particles per cu. ft. If in each day the air contamination continued at this level for the fourteen daytime hours and at zero for the ten quiet night hours, then, on average, about twelve *Staph aureus*-carrying particles would have been inhaled per day by an adult respiring 500 cu. ft. of air, and one *Staph aureus*-carrying particle by a newborn child respiring 44 cu. ft. (Nelson, 1946)

The settling plate results give a measure of the danger from sedimentation of airborne infected particles on to the face and other exposed parts of the baby. A *Staph aureus*-carrying particle would be received

per 10 sq in of exposed surface in each two or three hours during a morning in the nursery

If a single infected particle, containing perhaps from 1 to 100 *Staph aureus* cells, be sufficient to initiate infection, then the amount of *Staph aureus* air contamination discovered in the hospital was clearly enough to account for a very high incidence of infection among the inmates, even for universal infection of the babies within a day or two of birth. On the other hand, it is sometimes argued that initiation of infection normally requires contamination by a large number of bacteria, and can seldom follow receipt of the small numbers which are transmitted by the air, then, it is suggested that the large number of bacteria which constitute an adequate infective dose will be transmitted most commonly by contact and handling. However, there are reasons why one should not too readily assume that especially large numbers of pathogenic bacteria are likely to be transmitted by contact. The experiments of Ostermann (1908) have shown that only a very small proportion, usually less than 1 in 10,000 of the bacteria on a contaminated hand are transferred to a clean hand by the act of hand-shaking. In the present investigation a series of "handling" tests were made with two profuse nasal carriers of *Staph aureus*, each test on a different day. The surface of a culture plate was heavily handled by the carrier with the fingers, knuckles and palmar eminences of both hands. *Staph aureus* was obtained on the plate in most tests in thirteen of fifteen tests with one carrier and in five of six tests with the other. However, the number of *Staph aureus* colonies obtained was small, it varied from 1 to 112 per plate and averaged only 13 per plate. These observations suggest that as a rule only small numbers of *Staph aureus* will be transmitted by contact with the contaminated hands of nasal carriers. Heavier infection by handling may well be caused by "deep" skin carriers, persons whose hands are colonised and not merely contaminated by the staphylococci (Gilliespie, Devenish and Cowan, 1939), however, such skin carriers are relatively uncommon.

The anterior nares constitute the main natural habitat of *Staph aureus*, presumably this is the site most favourable to the initial establishment of colonisation. It is thus suggested that the spread of *Staph aureus* is in the first place mainly airborne, a small number of staphylococci being inhaled, caught in the anterior nares and there greatly multiplied. From the infected nose of an infant, large numbers of staphylococci may then be spread during bathing and toilet to skin abrasions, the conjunctiva and other susceptible parts of the body where they give rise to clinical infections.

The main source of the staphylococcal contamination of the hospital air was probably dust from bedding (Bourdillon and Colebrook, 1946), from personal clothing (Duguid and Wallace, 1948) and from handkerchiefs (Dumbell, Lovelock and Lowbury, 1948). In view of our previous finding that very little *Staph aureus* contamination of air was

produced by the sneezing of nasal carriers (Duguid and Wallace, 1948), we conclude that the air infection was not due in any important degree to the secretion droplet-nuclei described by Chausse (1913) and Wells (1934)

SUMMARY

(1) THROUGHOUT sixteen weeks during an outbreak of *Staph aureus* infections in a maternity hospital, the bacterial content of the air in two nurseries, a mothers' ward and a washroom was repeatedly observed by use of a slit sampler and of settling plates

(2) Air contamination with small numbers of *Staph aureus* was present almost constantly, being found in at least one room on forty-three out of forty-seven days on which examinations were made

(3) During seven mornings a total of 2125 cu ft of air was taken by the slit sampler from the nurseries and ward. On average this contained 0.04 *Staph aureus*-carrying particles per cu ft, these comprising about 0.7 per cent of all bacteria-carrying particles collected. On this basis it was calculated that while residing in the hospital an infant would inhale about one *Staph aureus*-carrying particle per day, and an adult about a dozen.

(4) Observations made with settling plates showed that during the mornings *Staph aureus* particles were falling from the air at the average rate of 0.46 particles per 10 sq in per hour.

(5) Experiments were made in which culture plates were heavily handled by nasal carriers. Only small numbers of *Staph aureus* colonies were obtained on each plate. It was concluded that *Staph aureus* would not be transmitted in much larger numbers by contact and handling than by the air.

We are indebted to Professor T. J. Mackie for his interest and advice.

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NOTES

I BEG to announce that the College at the Annual Meeting held on Thursday, 6th December, elected Dr William Alister Alexander as President, and Drs Leybourne Stanley Patrick Davidson, Douglas James Acworth Kerr, Douglas Nairn Nicholson, Ranald Malcolm Murray-Lyon, James Gilbert Murdoch Hamilton and Thomas Anderson as Members of Council, and that thereafter the College elected Dr Douglas James Acworth Kerr as Vice-President

The Council of the College elected the following Office-Bearers — John Alastair Bruce, T D, *Treasurer*, J Halliday Croom, M B, *Secretary and Registrar*, D M Lyon, M D, *Honorary Librarian*, Alexander Macfie, W S, *Clerk*, H J B Dunlop, C A, *Auditor*

NEW BOOKS

Any Questions? From the *British Medical Journal* Pp xii+240 London British Medical Association 1951 Price 7s 6d

This booklet is a collection of the more interesting questions and answers taken from the *British Medical Journal*. It is grouped systematically, each section containing a brief summary of recent advances, views on controversial problems and explanatory notes on medical terminology. This book is ideally suited for bed-time browsing, the only drawback being its brevity, but this year's popularity may well stimulate the editors to correct this rare fault in future volumes.

Clinical Urography—An Atlas and Textbook of Roentgenologic Diagnosis By WILLIAM F BRAASCH, M D, and JOHN L EMMETT, M D Pp v+736, with 1361 figures London W B Saunders Company Price 125s net

This excellent publication is precisely what its sub-title claims it to be.

From the wealth of the radiological files of the Mayo Clinic the authors would appear to have included examples of each and every variant of normal and pathological urogram. These are reproduced with a clarity of illustration and description which makes this a most readable and instructive volume.

The book is planned on a pathological rather than an anatomical basis, and each chapter concludes with an extensive but deliberately selected bibliography. The text includes detailed notes of the technique employed in the various methods of examination by which the radiograms were obtained. These methods include demonstrations of the radiological value of vascular patterns obtained by aortography and the examination of the genital tract in the male.

This is a most comprehensive volume, and is one which, in the opinion of the reviewer, fills a long-felt gap in the urologist's library. It is not only a valuable textbook for the post-graduate student but is a complete guide and reference work on the subject for the practising surgeon.

The volume is, of course, produced and bound in the manner we have grown to expect of the W B Saunders Company.

Child Care By AGATHA H BOWLEY Pp xii+203 Edinburgh E & S Livingstone Ltd 1951 Price 10s 6d net

Any person interested in the care of children will appreciate Agatha Bowley's new book. In it she gives an admirable account of the various ways in which illegitimate children may be brought up, together with details of the relevant Acts of Parliament and a useful bibliography.

Health and the Citizen By JOSEPH V WALKER Pp 158 London Hollis & Carter 1951 Price 10s 6d

This is a thoughtful and thought-provoking book written by a medical officer of health who has learnt from his own experience that medicine is concerned no less with Welfare than with Health. The author writes of the family as the social unit and considers those factors which, in an industrialised, urbanised society, affect its health and welfare. He has wise things to say concerning the problems created by the ageing of the population and considers work and play, neighbourhood and community, in their medical aspects. His therapy for very many of the more serious sicknesses from which a modern society suffers is derived not from the *British Pharmacopœa* but from the Bible, and not from the Old Testament but from the New.

The Physician as a Man of Letters, Science and Action By T K MONRO Pp 259 Edinburgh E & S Livingstone 1951 Price 25s

This attractive volume is virtually a dictionary of eminent medical men who have distinguished themselves in various fields, and is a revised and enlarged edition of a book which appeared in 1933. It does not claim to be complete, and the reader will seek in vain for Paracelsus, Vesalius and Harvey. On the other hand, he will make the acquaintance of many new friends, rescued by the author from an unaccountable obscurity. Most of the potted biographies consist merely of a few sentences, but it is not surprising that Professor Monro allows his pen to run on, as he deals with such giants as Sir Thomas Browne and Sir William Osler. The arrangement of categories has been accomplished with much skill: they are twenty-five in number, proceeding from poets and dramatists, through literature, law, philosophy, science, sport and even crime, until at length we meet "Some students of medicine who never qualified," among them Darwin, Galileo and Goethe. It is interesting to find among the literary doctors, Harry Roberts, Dan McKenzie, and that favourite of those who were boys in the nineties, Gordon Stables. This is certainly not a book which can be read from cover to cover. Yet it is not merely a reference work, and it is never dull. An ideal bedside book, it will enable many a tired doctor to end the day in company with the immortals, even though the claims of some of them to immortality are hardly enviable. Among the pirates is Thomas Dover, among the criminals, Hawley Harvey Crippen, and, although it seems hardly fair to place him in such company, Alexander Cameron of Lochiel. Although not illustrated, the volume is well produced, and there is a good biographical index as well as a general index.

Patterns of Disease as a Basis of Physiologic Pathology By FRANK L APPERLY, M A, M D, D SC, F R C P Pp xiii+456, with 87 illustrations London J B Lippincott & Company 1951 Price 63s net

The author has written a book combining applied physiology with pathology. Each disease is presented in its initial stages and each step in its progression is followed. The biochemical changes are discussed first and then the altered function, altered anatomy and the final cure or death. The compensatory mechanisms adopted by the body throughout these diseases are discussed fully yet concisely. The diagrams are clear and the illustrations excellent.

This book can be highly recommended to both undergraduate and post-graduate

Brompton Hospital Reports, volume XIX 1950 Pp vii+199 To be had from the Secretary, Brompton Hospital, London, S W 3 Price 12s 6d

This volume consists of eighteen papers most of which have already appeared in recent medical journals. Two, however, are published here for the first time. These are an article on "Education and Management of the Sanatorium Patient" and a valuable ten year follow up of patients with empyema complicating artificial pneumothorax. Most of the papers deal with diseases of the chest. This valuable publication is a great credit to the Staff of the Brompton.

Systemic Ophthalmology Edited by ARNOLD SORSBY Pp xiv+712, with 38 colour plates London Butterworth & Co (Publishers) Ltd 1951 Price 84s net

This book, the work of thirty-four contributors, may best be described as a collection of monographs covering a variety of subjects in the wide field of ophthalmology in relation to general medicine

Although, as is stated in the preface to this volume, the field covered by *systemic* ophthalmology has probably become too large to be covered satisfactorily by either a physician or by an ophthalmic surgeon, the alternative selected in this case, namely to seek the collaboration of more than thirty authors, can hardly fail to result in a lack of continuity of thought and outlook, features which were so essential a part of the great medical textbooks of the past While certain sections of this book are authoritative summaries of present-day knowledge, others are more superficial in their approach and detract from the value of the book as a whole The section on the relationship of prematurity to ocular anomalies in post-natal development is an excellent summary of the problems which may confront the clinician, particular attention being paid to the subject of retrolental fibroplasia Chronic bacterial infections such as tuberculosis, sarcoidosis and brucellosis are discussed in a chapter which is not only authoritative but most beautifully illustrated, and the chapters on endocrine disorders and cranio-cerebral injuries, as they affect the eyes, are also excellent

There is no doubt that this well-produced volume contains much that will be of interest and value both to the physician and to the ophthalmic surgeon

The Versatile Victorian By ZACHARY COPE, M D Pp xi+179, illustrated London Harvey & Blythe 1951 Price 12s 6d

Sir Henry Thompson, Bart, lived from 1820 to 1904, thus covering the whole of the Victorian era He was born of a middle-class family and was unequipped with the advantages gained from education at a public school or University, yet rose by his own ability and effort to a position in which he mingled with ease with the most distinguished people of his generation and he left his mark upon the Victorian Age

Thompson turned to surgery and specialised in urology The author traces his career from student days at University College Hospital through the various stages of advancement till he became a leading consultant and the friend of royalty This versatile surgeon had many interests other than his profession and it is necessary to deal with these separately Thus there are chapters on the connoisseur and dilettante, the artist, the writer, the traveller and the social reformer The story covers a period of wonderful advances which revolutionised surgery and raised the status and importance of the profession It also gives a wonderful picture of Victorian England and the great men of the day The author is to be congratulated on the production of a first-class biography of an outstanding surgeon and a man of many parts

Atlas of Histologic Diagnosis in Surgical Pathology By KARL T NEUBUERGER, with a section on Exfoliative Cytology by WALTER T WILLE Pp x+460, with 880 illustrations London Baillière, Tindall & Cox 1951 Price 84s net

The histopathologist is continually being confronted with new problems for reasons such as rarity of the disease, unfamiliarity with the field or unusual nature of the cellular reaction Consequently, a series of photomicrographs with appropriate legends covering routine surgical practice so widely as is achieved in this volume will find acceptance with the histopathologist at all stages in his career Reference is facilitated by a regional arrangement and ample index, while a section on exfoliative cytology adds topical prestige Photography and reproduction are good, but a future edition might with advantage include suitably selected subjects in colour

NEW EDITIONS

Oral and Dental Diseases By HUBERT H STONES, M D, M D S, F D S, R C S
Second Edition Pp xix+1011, with 959 illustrations, 91 in colour Edinburgh E & S Livingstone Price £5

This excellent book, first printed in 1948, is now deservedly in its second edition

While the main features remain as before, all the chapters have been revised and brought up to date by the addition of new material and by the inclusion of the latest references The chapter on the etiology of dental caries has been rewritten and this difficult subject is now presented in a form which is comprehensive and concise

The chapters on malocclusion of the teeth, maldevelopment of the jaws, stomatitis and allied diseases of the oral mucosa, odontomes and tumours, have all been amended and partially rewritten and there is little doubt that a considerable improvement has resulted

One great advantage of the book is that it is written in simple language and is, therefore, readily understandable by undergraduate students The fact that the whole field of oral pathology has been adequately covered makes it also suitable for post graduate students studying for higher qualifications

The publishers deserve to be complimented on the exceedingly high standard of their work, which has added greatly to the value of the book

Clinical Hematology By MAXWELL M WINTROBE, M D, PH D Third Edition
Pp 1048, with 220 illustrations and 17 plates London Henry Kimpton
1951 Price 90s net

A new edition of "Wintrobe" has come to mean quite an event in hæmatology and it is a pleasure to find this splendid textbook brought once again so completely abreast of the times Though enlarged by 180 pages, it retains its freshness as a balanced and critical presentation of the growing field of knowledge in blood disorders, and the important advances made since the last edition in 1946 have been woven into, rather than merely added to, the text Though essentially American in outlook, the extensive bibliography adequately covers the world-wide literature, and the volume remains a standard work for all interested in hæmatology

Principles and Practice of Obstetrics By J P GREENHILL and J B DE LEE
Pp x+1020, with 1140 on 864 figures London W B Saunders Company
1951 Price 60s

Under the authorship of J P Greenhill, this edition has been carefully revised so that its reputation, established in the days of the late J B De Lee, as an up to date book of reference, rather than a textbook, is maintained Numerous authorities have contributed sections on their special subjects, others have revised chapters for the author, or supplied data A bibliography is appended to each chapter Extensive summarisation of original articles, such as Sheehan's on Shock, duly acknowledged, are incorporated in the text, yet throughout, the author expresses his personal opinion on controversial matters, or his preference for a given technique when a choice is available With changing views and practices, it is difficult to know what to retain or discard in a new edition, and it is interesting to note that the passage of a metreurynter into the uterus in the treatment of placenta prævia is still illustrated and described in detail, albeit the text is in the small print used elsewhere for historical notes

Beautifully reproduced figures, of which 194 are in colour, liberally illustrate the text and are, as before, a valuable feature of this work

BOOKS RECEIVED

- BAILEY, HAMILTON, I R C S (ENG), F A C S, I I C S, F R S E Emergency Surgery Sixth Edition (*John Wright & Sons, Ltd, Bristol*) 21s Post 5d
- BECK, ALFRED C, M D Obstetrical Practice Fifth Edition (*Bailliere, Tindall & Cox, London*) 7s 6d net
- BLRNSTEIN, L, B S C, M R C S, L R C P, and WEATHERALL, M, M A, D M, B S C Statistics for Medical and Other Biological Students (*E & S Livingstone, Ltd, Edinburgh*) 18s net
- BLTT, W R Osler The Man and the Legend (*Wm Heinemann, Medical Books, Ltd, London*) 15s net
- CADÉ, SIR STANFORD, K B L, C B, F R C S, M R C P, F F R (HON) Malignant Disease and its Treatment by Radium Volume IV Second Edition (*John Wright & Sons, Ltd, Bristol*) 63s Post 1s 1d
- CARTWRIGHT, F F The English Pioneers of Anaesthesia (*John Wright & Sons, Ltd, Bristol*) 21s Post 7d
- Edited by CECIL, RUSSELL L, M D The Specialties in General Practice (*W B Saunders Company, London*) 72s 6d
- DERBES, VINCENT J, M D, F A C P, and WEISS, THOMAS E, M D Untoward Reactions of Cortisone and ACTH (*Blackwell Scientific Publications, Oxford*) 8s 6d net
- DUKE ELDER, SIR STEWART, K C V O, M D, LL D, D S C (ST AND), PH D (LOND), M D, F R C S, HON D S C (NORTHWESTERN), D M (UTRECHT) F R C S (EDIN), F A C S Volume V (*Henry Kimpton, London*) 90s net
- GEFFEN, DENNIS H, M D, D P H, and TRACY, SUSAN, M R C S, L R C P, D P H Hygiene, Infectious Diseases and Dietetics (*Longmans, Green & Co, London*) 9s 6d net
- HALL, I SIMSON, M B, CH B, F R C P E, F R C S E Diseases of the Nose, Throat and Ear Fifth Edition (*E & S Livingstone, Ltd, Edinburgh*) 18s net
- HERXHEIMER, HERBERT G J, M D FRANKFORT, L R C P E D, L R C S E D, L R F P S GLAS The Management of Bronchial Asthma (*Butterworth & Co (Publishers), Ltd, London*) 22s 6s net
- HOLMES, GORDON, M D, F R S Introduction to Clinical Neurology Second Edition (*E & S Livingstone, Ltd, Edinburgh*) 12s 6d net
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CLEARANCE TESTS OF RENAL FUNCTION

By C P STEWART, D Sc, Ph D

INTRODUCTION

IT is probably fair to say that clearance tests provide the most potent means at present available for the study of the normal mechanism of urine secretion as well as of abnormal renal function. This does not deny the fundamentally important contributions which other methods, often vastly different in character, have made in the past and may well continue to make in the future, but it emphasises the peculiar advantages of clearance tests for the study of renal function in living man. Nevertheless, clearance tests have their limitations (sometimes ill-defined or insufficiently appreciated) so that interpretation of the results of such tests can be difficult and may even be misleading. The aim of this lecture is to outline the basis and scope of clearance tests, and to point out some of the difficulties in technique and interpretation which at present limit their usefulness. It is an aim too ambitious for a single lecture because the subject is vast and rapidly growing, nor is any finality in sight with respect either to technique or to interpretation, yet I may hope at least to provide a bare outline with some hints which may indicate how the details may be filled in. And for a very full and masterly summary of the whole subject, may I at once refer you to Homer Smith's classic book on *The Kidney, Structure and Function in Health and Disease*. Had Homer Smith not, himself, been one of the great builders of our modern corpus of knowledge of renal function, we would still owe him an immense debt of gratitude for that book alone.

MODERN THEORY OF RENAL FUNCTION

It is desirable to begin by summarising the modern views on the mechanism of urine secretion since these views have been reached by considering evidence drawn from many, varied, sources and since they must, so long as they remain acceptable in the light of all existing evidence, be the basis for the interpretation of clearance measurements.

The glomeruli possess, in the endothelium of the glomerular capillaries and the basement membrane, a filter which offers no obstruction to the passage of small molecules of non-electrolytes or

small ions (except such as is imposed by the Donnan equilibrium) but retains macro-particles such as protein ions, fat droplets, and, *a fortiori*, blood cells. This filter, by a physical process, allows the formation of the "glomerular filtrate," in which the filtered substances are present in the same concentrations per unit volume of water as in the original plasma, except where the Donnan effect has interfered.

Glomerular filtration is thus envisaged as a *passive* process of which the rate depends on the area of the filter (the number of active glomeruli), the supply of material (rate of plasma flow to the active nephrons) and the filtration pressure (depending on the blood pressure, the osmotic pressure of the non-filterable particles, etc.), the separation achieved by the glomeruli thus depends for its driving force on cardiac activity. The *active* work of the kidney itself is done during the passage of the glomerular filtrate through the tubules. There some of the constituents are reabsorbed (*e g* water, sodium, chloride, glucose, urea, etc.) whilst others are increased in concentration by actual tubular excretion (*e g* creatinine, potassium). These activities are not continuous throughout the whole length of the tubule. Thus the proximal tubule reabsorbs water along with sodium ions (and their equivalent of chlorine ions) so that tonicity and *pH* remain unaltered, concentration and acidification of the urine occur in the distal tubule. Such finer points as these, and the question of the mechanism, which may perhaps involve enzyme activity, of the transport of molecules into and out of the tubule cells, are not yet of immediate importance to a consideration of renal clearance, however much they may become so in the future and however essential they may be, even now, for a full understanding of renal function.

RENAL CLEARANCE AND ITS MEASUREMENT

The concept of clearance, particularly as it has recently been developed, was implicit in the earlier work of Rehberg and even in the formulæ of Ambard, Addis and others designed to express the excretory capacity of the diseased, in relation to the normal, kidney. These workers, dissatisfied with the crude tests of renal function based solely on urine analyses, and realising the dependence of the rate of excretion of (*e g*) urea on the concentration in the blood had attempted to find some means of formulating the relationship. Indeed Addis conceived the idea that part of the blood flowing through the kidney might be regarded as passing unchanged, whilst the urea was completely removed from the remainder. Their efforts were further developed by Van Slyke and his collaborators who were the first to employ the term "clearance" which they defined as the volume of blood which must be cleared of urea to provide the amount excreted in the urine in one minute. The term "clearance" is perhaps analogous to the term "vitamin" the invention of which was so important in focussing attention on the "accessory food factors" which Hopkins had previously described.

Since it is the plasma which is filtered by the glomeruli, and since there is rarely (if ever) sufficiently free and rapid interchange between the blood cells and the plasma for the former to be appreciably "cleared" during passage through the kidney, it is now customary to consider *plasma* clearances and to extend the term to describe the excretion of any substance. Obviously the clearance can only be virtual and not actual, for all the blood flowing through the kidney is partially cleared instead of some of the blood being completely cleared as the definition suggests. It is perhaps preferable, therefore, while retaining the well-established term, to define it as the rate of excretion of the test substance in relation to the concentration of that substance in the plasma.

With either definition, if V is the volume of urine produced per minute, U_x the concentration of substance x per ml of urine and P_x the concentration per ml of plasma, the amount of x excreted in one minute is $U_x V$ and this amount is contained in $\frac{U_x V}{P}$ ml of plasma, so that this final expression represents the *plasma clearance* of x .

The determination of plasma clearance demands the measurement of V , U_x and P_x . It is necessary to obtain V by collecting urine over a not very prolonged, measured, period of time, the bladder being completely emptied at the beginning and end of the period, this necessity has led to the very general use of catheterisation with careful saline rinsing of the bladder. During this collecting period, P_x must be constant or must alter in such a way that its mean value during the period can be calculated, this has led to the practice, when dealing with "foreign" substances of giving an intravenous "priming" injection of the test substance and thereafter maintaining a constant P_x by infusion at constant rate. These technical procedures militate against the wide use of clearance determinations except for research purposes and, with the object of developing procedures more suitable for routine diagnostic purposes, many attempts have been made to simplify the technique. One of these will be discussed later. Where it is desired to measure the clearance of a normal urine constituent (e.g. urea) of which the plasma concentration can be induced to remain nearly constant over a long period, it usually suffices to collect urine over so long a time (e.g. 60 for 120 mins) that errors due to incomplete voluntary emptying of the bladder are minimised, and the simple technique of the "Van Slyke Urea Clearance Test" is satisfactory for ordinary purposes.

THE SIGNIFICANCE OF CLEARANCE MEASUREMENTS

The "maximal" $\left(\frac{UV}{B}\right)$ and "standard" $\left(\frac{U\sqrt{V}}{B}\right)$ urea clearance formulæ of Van Slyke and his collaborators suffice to give useful information concerning the renal functional efficiency, although the

latter of these expressions is somewhat artificial, it does not represent a real clearance but only an approximate prediction of what the clearance would be if $V = 10$, based on the assumption that for values of V below 20 c.c./min , the clearance is proportional to \sqrt{V} .

Measurement of the urea clearance, or indeed the measurement of the clearance of any substance can, by itself, give no information about the mechanism by which the test substance is excreted or, consequently, about the efficiency of the individual parts of the mechanism. That becomes possible only if a standard of reference can be found—a clearance measurement which assesses one single part of the excretory mechanism. Since glomerular filtration is an essential step in the excretion of every substance however it may be treated in the tubules, it is measurement of the glomerular filtration rate which is fundamental to the interpretation of all clearance measurements. Briefly, it is obvious that if a substance can be found to be filtered completely by the glomeruli but to be quite unaffected (whether by reabsorption or active excretion) by tubular activity, the amount of that substance excreted in the urine each minute (UV) is the amount filtered per minute by the glomeruli, and its clearance $\left(\frac{UV}{P}\right)$ therefore represents the volume of plasma filtered per minute—

the glomerular filtration rate. Equally obviously, any substance having a clearance lower than that of this standard substance must be partly reabsorbed by the tubules, anything with a higher clearance must have been additionally excreted by the tubules. It is presupposed that if a substance is reabsorbed by the tubules it is not excreted by them, and conversely that there is no reabsorption of a substance which is excreted by the tubules. It is on this basis that clearance tests are currently interpreted. The supposition is, however, not universally accepted and it is possible that the observed reabsorption (or excretion) really represents the resultant of both processes, one substance being reabsorbed to a greater extent than it is excreted, whilst another is predominantly excreted.

Glomerular Filtration Rate—The first to appreciate this seems to have been Rehberg who, chiefly because it was concentrated in the urine to a greater extent than any other known substance (at that time—1926), recommended creatinine, after administration of a test dose, as a measure of glomerular filtration rate. Although there is strong evidence that, in man, creatinine can be excreted by the tubules, the reliability of this substance is still under dispute, and the reference substance most usually employed is inulin. This fructose polysaccharide with a true molecular weight of about 5000 and a diffusion coefficient corresponding to an apparent molecular weight of 15,000, was suggested independently by Richards, Westfall and Bott, and by Jolliffe and Smith, its establishment as the generally accepted means of measuring glomerular filtration rate is largely due to Smith and his co-workers.

Effective Renal Plasma Flow—It will be necessary at a later stage to discuss the validity of the claim that inulin permits measurement of the glomerular filtration rate but for the moment it may be accepted. Consideration of the reasoning which led to appreciation of the circumstances in which glomerular filtration rate can be determined shows that a second standard of reference is at least theoretically possible. If there exists a substance which by glomerular filtration supplemented by tubular excretion is completely removed from the plasma during one passage through the kidney, so that all the plasma supplied to the functioning nephrons is "cleared," the clearance of that substance must be equal to the effective renal plasma flow. Such a substance, it is claimed, has been found in diodone and in *p*-amino-hippuric acid, provided in each case that the plasma concentration is low (1-5 mg/100 ml). The value of determination of the effective renal plasma flow lies in the power it gives of deciding such questions as whether a lowered glomerular filtration rate is due to deficiency of the filter bed itself or to a defective blood supply.

Tubular Excretory Capacity—On this basis other clearance measurements begin to assume importance. Thus, if the plasma concentration of diodone is progressively increased, the tubules become unable to excrete all the diodone presented to them until ultimately they are working at maximum capacity and still fail to clear the plasma completely. Under these conditions of tubular "saturation" the amount of diodone in the urine per minute ($U_D V$) is equal to the amount filtered by the glomeruli *plus* the maximum amount which the tubules can excrete. The contribution of the glomeruli is obviously given by the product of the glomerular filtration rate (which may be taken as the inulin clearance (C_{In})) and the plasma diodone concentration P_D . Hence the maximum tubular capacity for excreting diodone (usually termed the "active tubular mass" for diodone and represented by the symbol " T_{mD} ") is $U_D V - C_{In} P_D$. In practice it is necessary to modify this expression to allow for the facts that only a fraction (F) of the diodone is free and filterable (the remainder being bound to protein) and that although the concentration P_D is actually determined in plasma, the diodone is actually dissolved in the plasma water which constitutes a fraction (W) of the total volume, with these corrections the formula becomes $T_{mD} = U_D V - FWC_{In} P_D$. Fortunately there is evidence that the T_{mD} reflects the excretory capacity of the tubules for other substances so that its determination is of general as well as specific value.

Tubular Reabsorptive Capacity—Similarly, the absorptive capacity for various substances can be found. Thus glucose, normally, does not appear in the urine because the tubules are able to absorb the whole of the glucose presented to them by the glomerular filtrate ($C_{In} P_C$ per minute). If the plasma concentration (P_G) is sufficiently raised, the tubules though working to their full capacity will be unable to absorb all the glucose, and some ($U_G V$ per min) will reach the final

urine Hence the maximal absorptive power of the tubules for glucose (T_{mG}) is the difference between the amount presented and the amount ultimately excreted—i.e. $(C_{In} P_G - U_G V)$

Derived Ratios—Measurements of the glomerular filtration rate, the effective renal plasma flow and the tubular capacity for reabsorption or excretion provide the framework for elucidating the mechanism by which other substances are excreted or for investigating abnormalities of renal function It must be realised, however, that these standards of reference are to some extent interdependent (apart from any mutual interference of the test substances which may introduce errors of measurement) Thus the inulin clearance may be subnormal because of some inherent defect in the glomeruli or because of some failure in the supply of plasma to them, these could be differentiated only by taking into account the renal plasma flow The ratio glomerular filtration rate (C_{In}) effective renal plasma flow (C_D), which is usually termed the *filtration fraction* would be normal if the blood supply were at fault but low if the glomeruli themselves were functionally defective

Similarly the ratio between the effective renal plasma flow and the maximum tubular excretory capacity (i.e. C_D/T_{mD}) may be interpreted as expressing the volume of plasma which may be supposed to be cleared of the test substance per unit of functioning tubular tissue A fall in this ratio may be interpreted as indicating relative ischæmia

A measure of the tubular efficiency in relation to the rate at which glomerular filtrate is supplied to them is given by the ratio between the glomerular filtration rate and the maximum tubular excretory capacity (i.e. $C_{In} T_{mD}$), a high value would indicate tubular involvement (whether inherent or due to some aberration of supply to the tubules not affecting the glomeruli) more clearly than would a low T_{mD} alone

More complex formulæ based on the filtration rate, the mean arterial blood pressure, the renal blood flow, the plasma protein concentration and the renal venous pressure have been claimed to permit separate estimation of the afferent and efferent arteriolar resistance to the renal blood flow

Normal values for these functions and measurements are given in Table I

CLEARANCE TESTS IN CLINICAL MEDICINE

The clearance tests which have just been described are, it must be admitted, far too elaborate for everyday routine use when the only information desired is an answer to the question "is there kidney disease or is there not?", for that purpose much simpler procedures, amongst which must be numbered the Van Slyke urea clearance test, suffice Nevertheless their value is by no means confined to the elucidation of problems in pure renal physiology As research weapons, they have yielded information of the utmost value to the clinician in disentangling the abnormalities which make up the various

diseases he has to diagnose and treat. Every renal dysfunction must consist essentially of an imbalance of glomerular and tubular activities either intrinsically or through the associated extra-renal factors, and the real nature of such an imbalance can only be understood by a study of the discrete parts of the renal mechanism, that is, by renal clearance tests.

TABLE I

Normal figures for Plasma Clearance and Derived Ratios in Man (adult males). The clearances for adult females are somewhat lower, but the ratios are the same. These figures, from Smith's book are from his own laboratory, using the constant infusion method and are corrected to 1.73 sq m body surface (the conventional size correction) and 98.5° F rectal temperature.

	Mean	Standard Deviation	Units
C_{In}	131.0	21.5	cc/min
C_D	697.0	136.0	
C_{PAH}	654.0	163.0	
T_{mD}	51.8	8.73	mg/min
T_{mPAH}	79.8	16.7	
$C_{In}/C_D \times 100$	19.2	3.5	
C_D/T_{mD}	14.0	2.16	
C_{In}/T_{mD}	2.63	0.344	

Time permits of no more than one example illustrating the clinical value of clearance studies, though many more could be given—the problems of essential hypertension, of the abnormalities comprising the “lower nephron syndrome,” and of salt balance in chronic nephritis, to mention only three of considerable interest and importance. Let us, however, contrast the typical findings in acute glomerulonephritis and in pyelonephritis, both possibly of bacterial origin (although different organisms, acting in different ways, are incriminated) but the one with the glomeruli primarily affected, whilst in the other tubular degeneration occurs first.

In acute glomerulonephritis the inulin clearance is, of course, reduced, for it measures at least approximately the glomerular filtration rate. The effective renal plasma flow, as measured by diiodone clearance may also be reduced to a variable extent but the filtration fraction is markedly low (in spite of the hypertension) indicating the existence of loss of functional activity by the glomeruli themselves. The T_{mD} is also low as a rule, and may be very low in a severe acute case or in the terminal stages of a chronic glomerulonephritis. Nevertheless, the ratio C_{In}/T_{mD} is well below the normal level, further indicating that the glomerular filter bed is especially affected. Indeed, the residual functioning tubular tissue is capable of showing at least the normal excretory activity, for the ratio C_D/T_{mD} is usually normal or even high. With tubular activity maintained at a level closer to the normal than is the glomerular filtration rate, there is relatively little interference with the acidification of the urine (largely

a function of the distal tubule) and therefore little tendency to acidosis. On the other hand, the reduction in the amount of filtrate presented to the relatively active tubules per minute results in excessive reabsorption of sodium and chloride with, therefore, a tendency to œdema, whilst excessive reabsorption of urea combined with the diminished filtration may be an important factor in the elevation of the blood urea. Similarly inefficient filtration accounts for the decreased potassium excretion and the high plasma potassium levels so frequently found in severe acute glomerulonephritis.

The impression one gets is of a slow trickle of glomerular filtrate through relatively active tubules which therefore produce exaggerated modification of the filtrate.

The picture is quite different in pyelonephritis with its easily-produced acidosis, its dehydration, its absence of hypertension and œdema. Here the fault lies primarily with the tubules, and although the glomerular filtration rate, as indicated by inulin clearance, is somewhat below the normal, the effective renal plasma flow (C_D) is proportionately reduced so that the filtration fraction is normal. This, especially in the absence of hypertension which might conceivably have partially compensated for glomerular failure, shows the fault in filtration to be extra-renal, probably the dehydration is a causative factor. The tubular excretory capacity, measured by T_{mD} or T_{mPAH} , is very low, so that the ratio C_{In}/T_{mD} is abnormally high. In other words, the tubules are incapable of dealing adequately with even the reduced volume of glomerular filtrate which is supplied to them. As one consequence of this failure, the urine is improperly acidified, fixed base is inadequately conserved, and acidosis occurs very easily. The failure to conserve sodium means the excessive excretion of this ion with its attendant anions (mainly chloride), and therefore a tendency to salt depletion and secondary dehydration. It is possible that the tubular damage may affect even the passive reabsorption of urea, for the urea clearance in relation to the glomerular filtration rate is occasionally high, and, in the earlier stages or less severe cases the blood urea rarely rises much above the normal level. As the disease progresses, of course, glomerular degeneration occurs, filtration diminishes and, when the inulin clearance has eventually fallen to below a quarter of the normal, the symptoms of uræmia may begin to appear.

The typical picture is of a relatively rapid and copious stream of glomerular filtrate supplied to badly damaged tubules which are quite unable to carry out the normal amount of modification by reabsorption and excretion.

LIMITATIONS OF RENAL CLEARANCE TESTS

Enough has been said to demonstrate the value, for an understanding of renal disease, of the detailed examination of discrete renal functions which is permitted by clearance tests. Even a cursory examination of any section of the vast literature which has, in no more

than twenty years, been devoted to discussion of these tests, shows that their limitations are serious. Many things conspire to make the interpretation of the measurements a matter, at times, of very considerable difficulty and even doubt. In part, the complexity of the renal functions and of the impact of many extra-renal phenomena upon them, accounts for this. But in addition there is the question

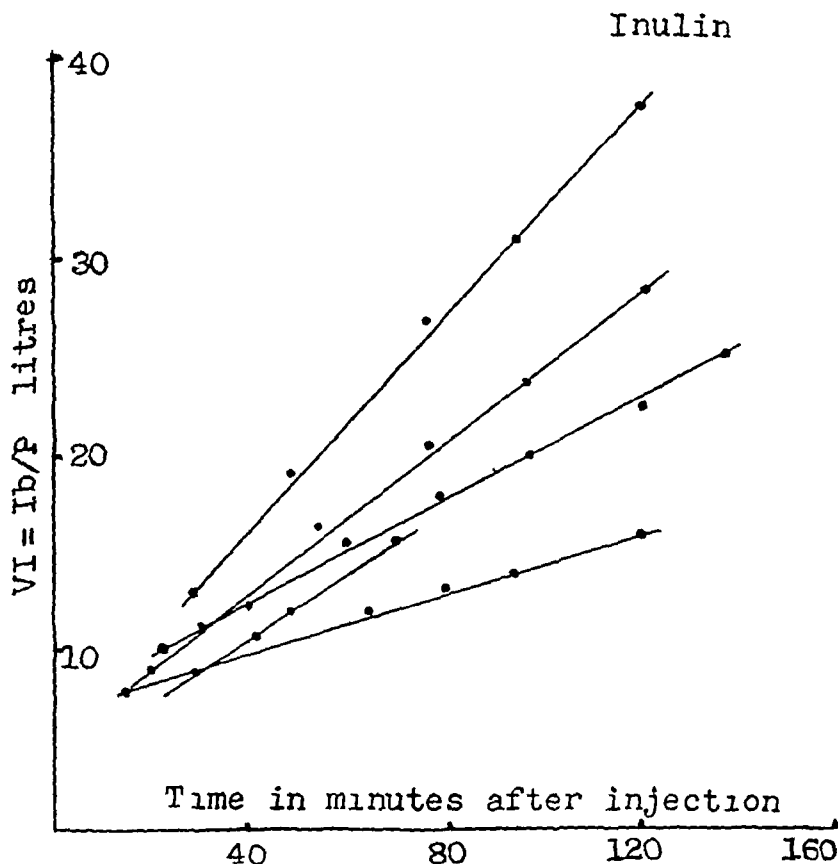


FIG 1a—The changing value of the expression —

$$\frac{\text{Amount of test substance remaining in the body (Xb)}}{\text{Plasma concentration of test substance (P)}}$$

in five subjects after a single intravenous injection of inulin

of whether the standards of reference which purport to provide the means of measuring the individual parts of the excretory mechanism are sufficiently accurate under all circumstances. Moreover the technical difficulties of the measurements themselves make it difficult to undertake (or to subject the patients to) the frequent observations which would be desirable in so many cases.

Technique—On the technical side, many attempts have been made to avoid the necessity of giving a constant intravenous infusion of the test substance throughout the period of measurement, and of

collecting urine carefully timed and accurately measured over short periods of time, (a necessity which demands catheterisation) The very number of these attempts demonstrates at once the potential value and the difficulty of clearance tests There are reasons for thinking that the constant infusion method is capable of giving the most accurate

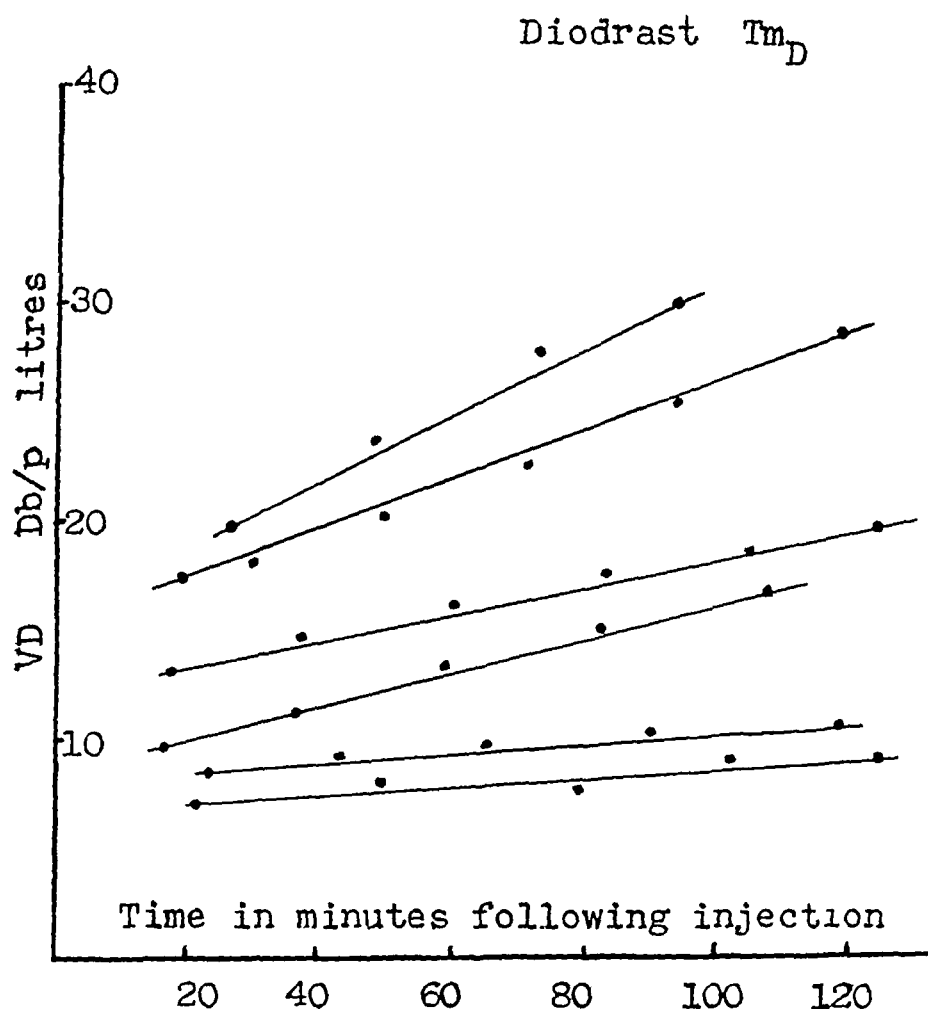


FIG 1b —The changing value of the expression given below Fig 1a —

For six subjects who received diodone

A maintained even distribution between plasma and extravascular fluid would give lines parallel to the base line in this and Fig 1a

results over the widest range of circumstances but where, as is often the case, the clearance is not rapidly changing and the water distribution in the body is reasonably constant so that the time of measurement can safely be increased, my collaborators and I believe that a simpler technique can be satisfactory Even the constant infusion method is imperfect in the respects mentioned for it demands three successive "clearance periods" of ten minutes each, and the water distribution may be modified by the considerable volume of fluid infused

The actual simplified procedure we have devised consists in giving, after a drink of water to promote urine flow, a single intravenous injection of the test substance—inulin, diodone, *p*-amino-hippuric acid, etc—of accurately measured amount. At two suitable, carefully noted times thereafter, samples of venous blood are collected and

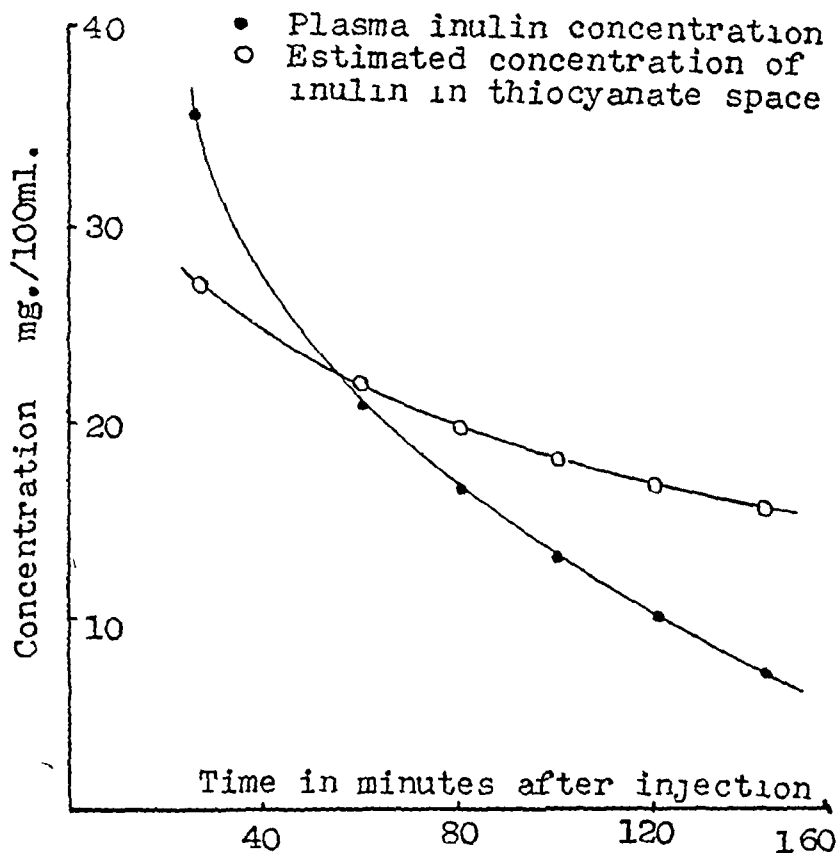


FIG 2—The changing concentration of inulin in plasma and extracellular fluid (calculated on the basis of thiocyanate space) after a single intravenous injection. Only at one instant in time do the concentrations coincide. This curve has the same significance as the lines in Fig 1 and is really another and perhaps more striking way of presenting the same data.

the bladder is emptied, the times (usually 30 mins for the first collection, 60 or 100 mins for the second according to whether diodone or inulin is being employed) are such that catheterisation is usually unnecessary. This simplification of technique depends upon recognition of the fact that with these substances and within these times, one cannot assume that equilibrium in the sense of an even distribution is reached and maintained between the plasma and extracellular fluid concentrations of the test substance. If equilibrium were reached and maintained thereafter, the amount of test substance remaining in the body at any moment divided by the concentration in the plasma

at that same moment would be constant, in fact under the conditions considered, this is not the case as is shown for inulin and diodone in Figs 1 and 2. On this basis, assuming that (as Fig 1 shows) the change in the value of the expression —

$$\frac{\text{Amount of X in the body}}{\text{Plasma concentration of X}}$$

is regular (i.e. linear), it is possible to derive formulæ for the calculation of the clearances. The derivation of these formulæ has been given fully elsewhere. They are —

Inulin Clearance —

$$C_{I_n} = \left[\frac{b (\log (P_I)_1 - \log (P_I)_2)}{\log (V_I)_2 - \log (V_I)_1} - b \right] \left[\frac{10^4}{10^2 - PP} \right]$$

Diodone Clearance —

$$C_D = \left[\frac{q (\log (P_D)_1 - \log (P_D)_2)}{\log (V_D)_2 - \log (V_D)_1} - q \right] \left[\frac{10^4}{10^2 - PP} \right]$$

Maximum Tubular Capacity for Diodone —

$$T_{mD} = (C' + m) \frac{(P_D)_2(V_D)_2^x - (P_D)_1(V_D)_1^x}{(V_D)_1^x - (V_D)_2^x}$$

In these formulæ —

$(P_I)_1, (P_I)_2, (P_D)_1, (P_D)_2$ = Plasma concentration of substance in first or second sample

V_I or V_D = (Amount of substance injected — Amount excreted) / Plasma concentration

$$b = \frac{(V_I)_2 - (V_I)_1}{t_2 - t_1}, \quad q \text{ (or } m) = \frac{(V_D)_2 - (V_D)_1}{t_2 - t_1}, \quad x = \frac{C' + m}{m}$$

$C' = FWC_{I_n}$ where F = filterable fraction of diodone and
 W = percentage water content of plasma = $100 - PP$

PP = plasma protein content

t_1 and t_2 = times of blood and urine collection (t_0 = time of injection)

Although they look complex their use is not really difficult, and involves much less expenditure of time and effort than does the manipulative and analytical work of the constant infusion technique. That agreement between this and the standard methods is good is shown in Table II which also shows, however, that in the case of diodone clearance the simple method employing venous blood gives lower results than the standard, this is not a serious disadvantage though it demands the use of a different normal standard and it can be overcome by using arterial blood for the analysis. With the development of suitable micro-methods, on which we are at present

engaged, it may become possible to use capillary blood and so abolish the difference

Apart from the impossibility of noting rapid fluctuations in clearance by the single injection method there are other possible objections to its use—e.g. when the plasma concentration of the test substance is altering, there must be a time interval before the alteration is reflected in the urine and this interval may vary with the rapidity of the change. However, under the specified conditions, agreement between the two methods is sufficiently good, and it becomes a matter of deciding the method to be employed for a given purpose according to the type of information required and the complexity of technique which is desirable or permissible. But it is obvious that the technique of clearance measurements has not yet reached perfection.

TABLE II

Typical examples showing agreement between clearances determined by constant infusion and those determined by single injection, but (necessarily) at a different time. The correction applied to the C_D figures is necessary, for comparison, to allow for the fact that venous blood was used in the single injection determinations, it is based on determinations of the arterio venous difference

C_{In}		C_D		
Infusion	Single Injection	Infusion	Single Injection Venous Blood	Single Injection + 20 per cent (Correction for Arterio venous Difference)
132	130	650	500	600
105	103	540	431	517
86	74	446	363	435
52	56	277	248	297

Standards of Reference—The difficulty of deciding upon test substances which will behave so precisely as the theory of renal function demands that they can be relied upon to measure accurately the rate of glomerular filtration, the effective renal plasma flow, etc., is indicated by the long list of such substances which have been tried and found wanting. For measurement of glomerular filtration rate inulin is now the most generally used substance, but there is evidence to suggest that it is by no means perfect. Indeed one may wonder whether there exists in fact any substance which is wholly filtered by the glomeruli without alteration in concentration and is absolutely unaffected by tubular activity. If inulin did behave in this way, the amount excreted per minute (UV) would be a constant multiple of the plasma concentration (P), so that if UV were determined for various values of P, and UV were plotted graphically against P the result would be a straight line passing through the origin. However, in 15 cases which we examined, using both the single injection and the constant infusion method, the straight line connecting the points when UV was plotted

against P did not pass through the origin. The relation between UV and P was given not by the equation $UV = KP$ but by $UV = KP - a$ (Fig 3). This afforded good evidence for believing that inulin is in fact partly reabsorbed by the tubules and that in normal people the true glomerular filtration rate is some 15 per cent

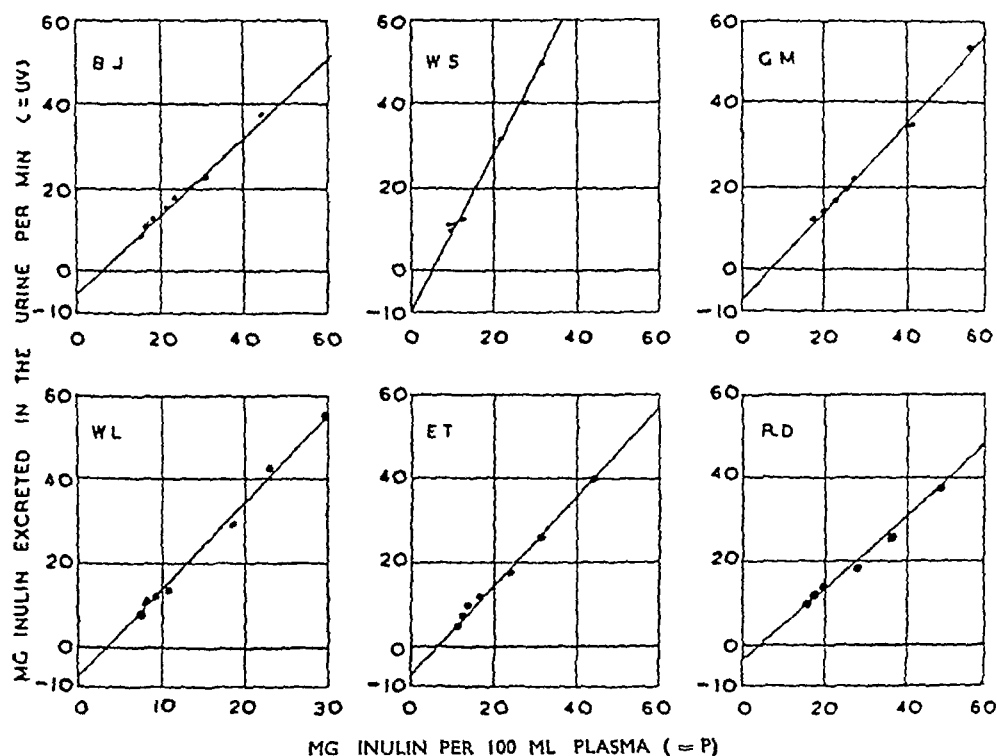


FIG 3 —The rate of inulin excretion (UV) plotted against the plasma inulin concentration (P)

If $\frac{UV}{P}$ were constant for all values of P , the lines would pass through the origin

higher than is indicated by the inulin clearance. It may well be that the discrepancy is greater when the kidneys are diseased, for we have found, in a few severe cases of chronic nephritis that the inulin clearance was lower than the urea clearance but that in the one case where the experiment was tried, the inulin clearance was markedly increased when the urine flow was forced to the maximum of which the damaged kidneys were capable. A similar abnormality of the C_{In}/C_{LREA} ratio has been reported by Raaschou in a few cases of pyelonephritis, and although a different explanation was advanced, there is evidently some dubiety about the validity of the claim that inulin provides a reliable and accurate measure of the glomerular filtration rate. For many purposes the approximation is doubtless sufficiently close, but the fact that the measurement is merely an approximation undoubtedly limits the usefulness of clearance tests by introducing some uncertainty into their quantitative interpretation.

There is, at least in the presence of severe renal damage, a similar doubt about the reliability of diodone and *p*-amino-hippuric acid as test substances for the measurement of effective renal plasma flow

If they are really completely excreted from the plasma during one passage through the nephrons, the "extraction ratio" (the ratio of the difference between the concentrations in arterial and renal venous plasma to the arterial concentration) should be 1.0. In health the extraction ratio does approach closely to 1.0 but in nephritis it may be as low as 0.5 or even less. This may mean that with destruction of the renal parenchyma more and more blood reaches the renal side from the arterial without passing over functioning tubular tissue, but this suggestion cannot be substantiated and the element of uncertainty persists.

Interference—For a strict comparison of clearances in a given individual, measurements ought to be simultaneous. This is especially true when the conditions under which the kidneys function are subject to rapid change. Yet the ideal is frequently unattainable, for one test substance may interfere with the excretion of another. This is of course particularly true of measurements of tubular activity. Tubular excretion appears to involve only two transport systems with a factor common to both, hence loading the tubules with a substance X to measure T_{mx} depresses the excretion of all substances in one or other of two groups. Even tubular reabsorption and tubular excretion may be mutually competitive for it has been found repeatedly that the simultaneous measurement of T_{mPAH} and T_{mG} gives low values for both (but—a further indication of the difficulties involved—this may be due to interference in the methods of chemical analysis).

Interference may be produced by extra-renal factors and although some of the curious results obtained when clearances are measured during hormone imbalance may be real in the sense that the imbalance specifically affects discrete parts of the renal mechanism, they may merely be due to extra-renal disturbances. Thus in one case with apparently normal renal function recently studied in my laboratory, the continued administration of ACTH resulted, on the fifth day, in a marked increase in the inulin clearance to a level far above the normal, whilst there was no accompanying increase in the urea clearance or the diodone clearance. The phenomenon may possibly be due to dilatation of the afferent arterioles with constriction of the efferent arterioles. At least it illustrates the difficulties in interpreting in such circumstances the results of clearance tests and therefore emphasises their limitations. Yet it also illustrates their value, for the demonstrated changes in renal activity, however produced, must be largely responsible for the alterations in the excretion of electrolytes and other substances which are so marked a feature of hormonal abnormalities.

Finally, it should again be emphasised that interpretation of renal clearances is based on the accepted theory of renal mechanism. There is little doubt that this theory is correct in broad outline, but it may (and probably will) be modified in detail as knowledge increases. In particular it seems doubtful whether the present view that one

substance is reabsorbed and not excreted by tubular activity whilst another is excreted and not reabsorbed will survive more complete examination of the transport systems. Also, it may become necessary to take more cognisance than has hitherto been done of the effects of the Donnan equilibrium and perhaps other physico-chemical factors in altering the composition of the plasma during glomerular filtration.

CONCLUSION

I am very conscious that this brief outline of the nature, uses, and limitations of renal clearance tests may by the omission of detail and of full discussion of many controversial matters, have failed to give a true picture. I hope, however, that I have succeeded in demonstrating that these tests provide a potent weapon which has already given a greatly increased understanding not only of renal physiology pure and simple, but of the varied derangements of renal function. And it should be reiterated that, with all their faults and limitations, we owe to them much of our knowledge of many other abnormalities besides those primarily due to renal disease, such as the serious disturbances of salt and water balance which occur in Addison's disease, congestive heart failure, Cushing's syndrome, and the like. Though not—as yet, at least—ordinary everyday “routine” tests they are steadily increasing our insight into the aberrations which make up many disease processes and they are therefore of the utmost value to the clinician who must appreciate, implicitly or explicitly, the mechanism involved in the disease he hopes to treat by a rational therapy.

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THE PATHOLOGY OF FŒTAL AND NEONATAL ASPHYXIA

By AGNES R MACGREGOR, M D , F R C P Ed

Lecturer in Pathology of Diseases of Children, University of Edinburgh

SIR JOSEPH BARCROFT, to whose work on foetal respiration we owe so much that is known of this subject, defined foetal asphyxia as " that combination of oxygen lack and carbon dioxide excess wrought by occlusion of the umbilical cord " (Barcroft and Barron, 1937-38) It is primarily a state of oxygen lack Other phenomena that may accompany this state, such as disturbance of carbon dioxide content, the production of organic acids and the development of acidosis, are secondary to oxygen lack and dependent upon it Many people, therefore, prefer the term " anoxia " to " asphyxia," though the purists object that the condition referred to is rarely, if ever, literally anoxia, and prefer the less familiar term " hypoxia " I am not greatly concerned about what term is used, so long as it is understood that the subject I am attempting to discuss is the causes and consequences of dangerous degrees of oxygen lack in the foetus and newly born child, in so far as these can be studied by the methods of the morphological pathologist

It is recognised that the tolerance of the foetus and newborn to anoxia is high compared with that of older subjects The ability to survive anoxia depends finally on the ability of the brain to survive, as this is, of all organs, the most vulnerable to anoxia It is believed that the effect of anoxia on the brain, including the medullary centres, is purely depressant, and although impulses reaching the brain from the chemoreceptors are increased by anoxia, these are of no avail when the medulla is so depressed that it is unable to respond Anoxic deaths are due to anoxic depression and death of nerve cells in the brain The immature brain of the newly born has a lower oxygen requirement, and consequently a higher tolerance of anoxia than the fully developed brain of the older subject Other factors in the higher anoxic tolerance of the foetus are an ability to utilise more completely such oxygen as is available, and a capacity for anaerobic respiration, by means of glycolysis, which makes survival possible for short periods under conditions of anoxia that would inevitably be fatal to an older subject

The causes of foetal anoxia are well known briefly they are these Interference with the circulation of blood through the placenta and cord, by prolapse, knots or twists of the cord, or by premature separation of the placenta , placental insufficiency due to infarction, disease or post-maturity , prolonged pressure on the foetal head during labour, causing

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anoxia of the brain by impeding venous return, and some anoxic conditions of the mother, such as anæmia, cardiac disease and anæsthesia. The risk to the foetus of asphyxiant anæsthetics is now recognised, and it seems that respiratory depression resulting from narcotic drugs is less dangerous than that due to anoxia.

The contribution that can be made to knowledge of this subject by the morphological pathologist is limited. The solution of most of the fundamental problems must be sought in those alterations of function and reactivity that lie for the most part beyond the reach of the histologist's methods. But the contribution that pathology has already made is not negligible, nor has the limit of what it may contribute yet been reached. This contribution is to reveal the magnitude of the problem in terms of loss of infant life, and to attempt to present morphological facts with which morbid changes of function can be correlated.

Asphyxia as a Cause of Fœtal and Neonatal Deaths—It is not unfair to claim that the present widespread interest in and concern about the results of foetal and neonatal asphyxia took origin in the revelations made by pathologists as a result of study of large numbers of autopsies in cases of stillbirth and early neonatal death. Such studies have invariably indicated a high prevalence of asphyxia in these fatal cases. In fact, nearly all intra-uterine, intra-natal and early neonatal deaths are anoxic deaths, so the problem of anoxia enters into nearly every problem of what is now being called "perinatal mortality." If one excludes cases in which anoxia is secondary to some other major cause of death (such as traumatic intracranial hæmorrhage) the number of deaths primarily attributable to asphyxia is still formidable. Among stillbirths it amounts to at least two-thirds of all cases. Among the liveborn, published work gives percentages varying from about 12 to 40 per cent of deaths during the first month of life, nearly all occurring within the first three or four days. If cases are included in which death is caused by certain lethal lesions (such as some forms of hæmorrhage) that are in all probability dependent, or partly dependent on anoxia, the percentage of neonatal deaths that can be attributed to anoxia is certainly not below the higher figure quoted, and probably exceeds one-half of all such deaths. And with the better control of infection and of trauma, which in recent years has eliminated so many neonatal deaths, the percentage due to asphyxia is now higher than even a few years ago.

The classical pathological appearance of death from asphyxia are seen to greatest advantage in dead-born foetuses at, near, or after term, in which the degree of anoxia has been very severe. In these cases the typical picture is one that is common to acute asphyxia at any age, with all the features very well developed, and with, in addition, certain other features that are peculiar to foetal asphyxia. The common features are universal venous engorgement, dark, fluid blood, delayed clotting, petechial hæmorrhages under the thoracic serous membranes, in the thymus gland and elsewhere, and a dilated heart. The features peculiar

to foetal asphyxia are those produced by inhalation of contents of the amniotic sac

Among physiologists who have studied foetal respiratory function it is generally agreed that the foetus, from an early stage of development, is capable of making movements resembling those of breathing. This was proved by Barcroft in sheep foetuses (Barcroft and Barron, 1937) and has been confirmed by others in various animals, and there is good evidence that it is true also of the human foetus. Barcroft (1934, 1947) described three types of respiratory movements, each representing a level of control by nervous centres. These he demonstrated by the study of foetuses at different stages of development, during which the effects of the three centres are added from below upward, and also by the study of the effects of cyanide poisoning in adult animals, by which the control of the three centres is progressively removed from above downward. As cyanide acts by preventing oxygenation of tissues, the results of these experiments are applicable to naturally occurring conditions of anoxia. When only the first developed, or lowest, centre is in control, the type of respiratory movement made is the "primitive gasp," an isolated movement of considerable depth. When the second level of control operates, the movements are of the type described by Barcroft as the "single prolonged inspiration" or "apneusis", and only when the third and highest centre takes control is regular, rhythmic respiration of normal type—"pneumotaxis"—established. All these types of respiratory movements can be performed by the foetus, and they can be elicited by various mechanical stimuli and as a response to anoxia. Thus far there is fairly general agreement. Opinions differ as to whether any of these movements occur *in utero* under normal conditions, and as to whether, if they do occur at all, the movements of pneumotaxis (which alone can be considered normal after early foetal life) are of sufficient amplitude to draw into the lungs the amniotic fluid that forms the intra-uterine environment of the foetus. Some answer both these questions in the affirmative, others in the negative, believing that the foetus is normally apnoeic, and that only the deeper movements released by anoxia are capable of causing aspiration of amniotic fluid.

The pathologist, attempting to interpret his observations, is placed in a quandary by this disagreement among the physiologists, and is thrown back on his own observations, which, in my experience, are these. Amniotic fluid is not difficult to recognise in the lungs of a foetus. The fluid itself has a low protein content and cannot be distinguished in histological sections from the fluid of transudates. But it contains in suspension solid debris that is readily identified: cornified squames and fine hairs from the skin of the foetus, fragments of epithelium from the amnion, and sometimes fibrin, blood and pus cells. The cornified squames especially, when present numerously in the lungs of a foetus or newborn infant, prove that amniotic fluid has been inhaled in quantity. It has been my experience that those

foetuses in which evidence is found of aspiration of large amounts of amniotic fluid are those in which the general evidence of asphyxia is most clear, and that those in which some other adequate cause of death is present and the general signs of asphyxia are slight or absent, are those in which evidence of aspiration is least likely to be found. Further, it seems certain that solid amniotic débris in the fine bronchi and alveoli cannot fail to obstruct air entry to some extent and thus to be injurious to the infant after birth. It has been argued (Snyder and Rosenfeld, 1937) that this solid material is present only when the amniotic fluid is abnormal, in that it contains an abnormal amount of débris, as when a severely asphyxiated foetus has passed meconium and this is aspirated along with the amniotic fluid. This accident does certainly increase very greatly the amount of débris that may enter the lungs (Fig 1), but I have found that amniotic fluid almost always contains enough solid débris to make it certain that much must be inhaled along with any fluid that enters the lungs. If continuous inhalation of amniotic fluid is really a normal occurrence, it would seem that all foetal lungs must contain great quantities of this solid debris. This is not so. I find myself, therefore, in full agreement with Windle's opinion (1950) that inhalation of liquor amni is not a physiological occurrence but happens only under conditions of anoxia in which the foetus makes abnormal respiratory movements of great amplitude. I therefore include the finding of amniotic débris in quantity in the lungs among the most important and reliable pathological signs of foetal asphyxia.

Thus far we have been considering the asphyxiated foetus that is born dead, in which intra-uterine anoxia has reached so severe a degree that the vital centres are paralysed and the functions of respiration and circulation cease before birth. We come now to consider asphyxia as a cause of the deaths of live-born infants in the early days of independent life. These may be considered in two groups. (1) Infants who are asphyxiated at birth and fail to establish and maintain a satisfactory respiratory function after birth, and (2) infants who have not obviously suffered from anoxia before or during birth and who may appear to be in reasonably good condition at birth, but who become anoxic subsequently, having failed to maintain oxygenation of their blood, and die usually within three days after birth.

Cases in the first group (infants born asphyxiated) represent merely another aspect of the problem of the anoxic stillbirth. The causes are the same, the pathological effects are of the same kind, but the vital functions are still possible, even though impaired. In these cases the fact of birth and the demand that the infant must now supply himself with the oxygen that he has hitherto received from his mother, introduce a new factor. If the medulla is so far depressed that it can no longer respond to the stimuli that normally produce the first breath and cause breathing to continue, resuscitation will fail and the child will speedily die. If, however, breathing is attempted, any amniotic fluid



FIG 1—Lung of asphyxiated fetus. Bronchus and alveoli filled with debris from amniotic fluid contaminated with meconium. H & E $\times 100$

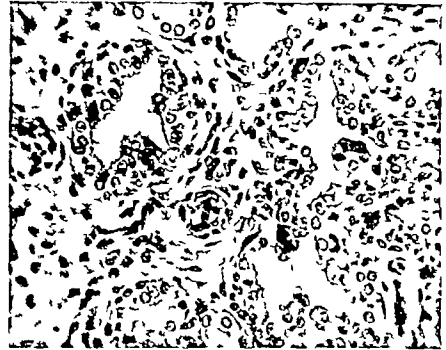


FIG 2—Lung of fetus of 850 gms. Air spaces lined by cubical cells and separated by thick septa of primitive mesenchyme. H & E $\times 425$



FIG 3—Lung of premature infant of 940 gms who survived one day. Overdistention of bronchioles with complete atelectasis of alveoli. H & E $\times 25$

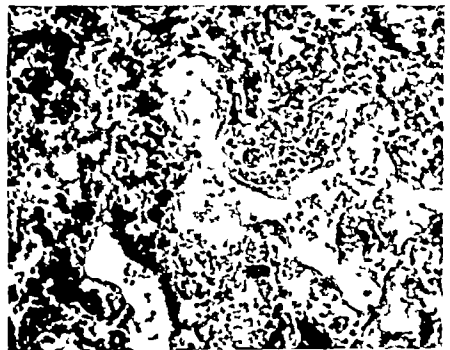


FIG 4—Lung of premature infant of 1800 gms who survived two days. Hyaline membrane lining alveolar ducts. Early inflammatory reaction. H & E $\times 160$

or debris that may be in the lungs, which hitherto has been harmless, now becomes a handicap to respiration and a menace to life, impeding aeration of the lungs and causing a progressively worsening anoxia. In severe cases of this type survival is usually short, but in less severe cases recovery is possible, or the child may die after some hours or days of precarious survival. Among such infants who ultimately succumb, as among the second group of infants who become anoxic after birth and die, there is a large preponderance of prematures. It would seem that the full-time infant, even though seriously anoxic at birth, if he is capable of beginning to breathe, usually contrives to get enough oxygen to allow him to break out of the anoxic vicious circle and survive. But the premature has far more difficulty both in establishing air breathing and in maintaining oxygenation, and is all too apt to be caught up in that vicious circle in which the more he is in need of oxygen the less he is able to get it into his blood. Neonatal anoxia is thus to a very large extent a problem of prematurity, and so it may be appropriate to consider some of the handicaps under which the premature baby is placed in his efforts to attain and maintain adequate oxygenation.

The first essential for adequate oxygenation is the possession of respiratory centres capable of performing their necessary function. It is often assumed that much of the respiratory difficulties of the premature derives from inefficiency of immature respiratory centres. There is some evidence from physiological studies that the respiratory centres of premature infants (including the chemoreceptors) are capable of prompt and vigorous response to their appropriate stimuli, but that their adaptability is less and that there may be difficulty in maintaining an adequate response to oxygen lack over any considerable period. There are, also, abnormalities of respiration that are common in the premature, such as periodic breathing with periods of apnoea. Whether any of these peculiarities should be attributed to immaturity of the centres or to some other factors is not known.

The second essential for adequate oxygenation is the possession of a respiratory apparatus properly adapted to procure ventilation of the lungs and oxygenation of the blood in them. In this respect the premature is demonstrably ill equipped. The chest wall is soft and flexible, the respiratory muscles are poorly developed and weak. Respiration is almost entirely abdominal and may produce very little movement of the thoracic wall. This is an obvious handicap to the child in the business of expanding the lungs. Further, the lungs themselves are poorly adapted to the function that has been untimely thrust upon them. At term, the development of the lungs is, for practical purposes, complete and their structure resembles in all essentials that of adult lungs. The distal air spaces, or alveoli, are perfectly developed, their walls are thin, fully vascularised, and equipped with their proper content of elastic fibres. Such lining cells as the alveoli still possess are flattened, and they form a discontinuous layer, through the gaps in which the capillaries in the alveolar walls

protrude, to come into direct contact with the air in two contiguous alveoli, thus facilitating to the greatest possible extent the exchange of gases between the inspired air and the blood. It is, however, only near normal term that the foetal lungs attain to this degree of structural perfection. In the early stage of its development the lung is formed by the budding and branching of the primitive bronchi into a mass of primitive mesenchyme. These, by progressive branching, form primitive ducts and canals, and only fairly late in development are true alveoli formed. At this incomplete stage of development, which still obtains when the foetus reaches what is regarded as viable age, and for some time thereafter, the most distal existing air spaces still retain a continuous lining of cubical epithelium, and an appreciable amount of the primitive mesenchyme persists in the septa between them (Fig 2). The capillaries in these septa are thus separated from the lumen of the air space by a certain thickness of this tissue and by a layer of thick cubical epithelial cells, which still remains continuous after expansion with air. And there is, at this stage, little or no elastic tissue in these septa.

It may be said, therefore, that, compared with the full-term infant, the premature has lungs that are more resistant to expansion, owing to the excessive thickness of the septa, less resilient, owing to lack of elastic tissue, and less well adapted for the exchange of gases, owing to the thickness of tissue between the capillaries and the air. It is reasonable to correlate these anatomical observations with the facts that a premature infant takes much longer than a full-term infant to expand its lungs completely, even when breathing is normal, and has more difficulty with the transfer of oxygen from the lungs to the blood.

Atelectasis in the premature may be a very important factor causing or aggravating neonatal anoxia. Pathologists are familiar with the picture of a premature baby who has lived for twenty-four hours or more, and whose lungs show at autopsy no visible aeration, sink heavily in water, and, on microscopical examination, show that no air has penetrated beyond the alveolar ducts, and even only to a few of those, so that one can only marvel that life was sustained for so long. These extreme cases are most usual when the child has suffered from anoxic depression at birth, or where some obstruction to air entry (*e g* by liquor amnii, or vernix, or hyaline membrane) exists in the respiratory passages or lungs. But even when the efforts to breathe are vigorous there may result a condition in which acute overdistension of the bronchioles is accompanied by complete atelectasis of the air spaces distal to them (Fig 3). Such a misfortune of mal-expansion is most likely when some cause of obstruction exists, or may easily be produced by ill-advised attempts at artificial inflation, but can result apparently from the infant's own efforts with lungs poorly adapted, by reason of immaturity, to their respiratory function.

Another common pathological condition in the lungs of the newly born that has a close bearing on neonatal anoxia is the pulmonary

hyaline membrane (Fig 4) It is found in about one-half of all premature infants who die in the first two weeks after birth, and in a smaller percentage (from 12 to 25 per cent according to different observers) of full-term neonatal deaths Most cases occur in infants that die between one hour and four days after birth It does not occur in the stillborn For long it was known as "vernix membrane," the name given to it by the Boston school led by Farber (Farber and Sweet, 1931) who believed that it was composed of vernix caseosa inhaled by the fœtus with liquor amnii This theory was generally, and perhaps too uncritically, accepted, and it is surprising that it held the field for so long, for if vernix, collected from the skin of a fœtus or from the liquor amnii, is processed in the same way as an ordinary paraffin section, it appears, when its fatty matrix has been removed, to be composed entirely of cornified cells having exactly the same appearance as those that form deposits in the lungs of asphyxiated fœtuses, and bearing absolutely no resemblance to the hyaline membrane During the past two years the vernix theory has fallen into disfavour and has been superseded by theories in surprising variety It has been suggested that the membrane is caused by injury of unspecified nature by an unspecified noxious agent, to the epithelial lining of the respiratory tract (Miller and Hamilton, 1949), that it is a product of lysis of the epithelial lining of the immature lung on expansion at birth, that it is a result of aspiration of acid gastric juice (Ahvenainen, 1950), that it is caused by administration of oxygen (Bruns and Shields, 1951), that it results from disturbed nervous impulses through the vagus (Miller, Behrle and Gibson, 1951) Quite recently, the Boston school (Blystad, Landing and Smith, 1951) has produced a revised version of the amniotic aspiration theory of Farber, suggesting that the membrane is formed from the protein content of amniotic fluid, concentrated after a period of air breathing and deposited in membrane form This theory, if proved, would restore this condition to its place among the effects of fœtal anoxia None of the new theories can be accepted until further study and experimental investigation have been carried out, and until the nature and origin of the membrane are certainly known it must remain in doubt whether or not anoxia is responsible for its production Nor is it surely known that it is a cause of neonatal anoxia, but histological study strongly suggests that it is The presence of hyaline membrane is almost invariably associated with severe atelectasis The membrane usually forms in alveolar ducts, and it appears to block the entrances to the more distal air spaces, preventing their expansion or causing them to collapse Sometimes the affected ducts become greatly over-distended, and interstitial emphysema may result, the whole picture being indicative of obstruction to the passage of air Moreover, in those air spaces to which air penetrates, the presence of a thick layer of membrane interposed between the air and the blood in the capillaries must surely interfere seriously with the exchange of gases It is therefore reasonable

to assume that the membrane is an additional handicap to respiration and a factor in producing or aggravating neonatal anoxia. It is not known how often infants thus affected survive, but it may be that the much higher incidence of hyaline membrane in the premature at autopsy is in reality due to a much higher survival rate among the mature.

The discussion of the pulmonary aspects of foetal and neonatal asphyxia cannot be completed without reference to pneumonia. The relation between foetal asphyxia and those cases of pneumonia that occur before or soon after birth is very close. In many cases the pneumonia is caused by aspiration of infected liquor amnii by an anoxic foetus, and in other cases the water-logged and ill-ventilated lungs of the newly born with anoxic depression and atelectasis provide a favourable site for the development of a post-natal infection. I have found that most of these anoxic infants who die on or after the third day have developed pneumonia. These cases of pneumonia are appropriately termed "post-asphyxial". The pneumonia must be regarded as secondary to the asphyxia, but it often causes the death of an infant who might otherwise survive.

Time will permit only brief reference to the relation of asphyxia to hæmorrhage, that other most important cause of foetal and neonatal death. Petechial hæmorrhages, as has been said, are among the recognised pathological signs of asphyxia, but there is some doubt about the role of asphyxia as a cause of major hæmorrhage. That the two are often associated is known to every pathologist, and it seems certain that some of the effects of asphyxia must favour hæmorrhage—the venous engorgement, the raised blood pressure, the delayed clotting of blood, the decreased capillary resistance. There are many forms of foetal and neonatal hæmorrhage in which it is by no means clear that direct trauma plays any part and it is more than likely that anoxia is, at the least, one of several factors that may be responsible. As an example may be cited intraventricular cerebral hæmorrhage. Although it is occasionally found in a stillborn foetus and in a full-term liveborn child, the usual victim is a small premature who has lived one to three days or sometimes longer. Often he has been anoxic at birth, though this is not invariably so according to the history. The source of the intraventricular bleeding is usually a hæmorrhage from a vein under the ependyma, rupture of which releases free hæmorrhage into the cavity of the ventricle. The hæmorrhage may thus occur in two stages, the first of which may well be related to anoxia in the same way as other petechial hæmorrhages, to which it is comparable. In similar fashion, small venous hæmorrhages under the capsule of the liver may progress to form a large hæmatoma, and ultimately, through rupture of the capsule, may produce massive and rapidly fatal intraperitoneal hæmorrhage.

It is evident, therefore, that many deaths may be attributed to infection, and many to hæmorrhage that ought properly to be laid to the account of asphyxia, which will then be revealed in its true role as the principal single cause of foetal and neonatal death.

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THE ASSESSMENT OF INADEQUATE LACTATION

By R A MILLER, M A , M D , Ph D , F R C P E

(From the Royal Hospital for Sick Children, Edinburgh)

FOR the diagnosis of inadequate lactation in women it is essential to know the signs and symptoms and tests which may be of value in the assessment of lactation. Since these signs, symptoms and tests have rarely been correlated a series of observations have been made on cases of inadequate lactation occurring in the Simpson Memorial Maternity Pavilion, Edinburgh.

SYMPTOMS AND SIGNS IN INADEQUATE LACTATION IN THE MOTHER

The clinical picture, prognosis and treatment of inadequate lactation in women depends on whether the condition is due to a fall in milk yield or to an increase in the infant's demands which exceeds the mother's maximum yield. The clinical picture due to a reduction in milk yield is most often seen in women between the second and sixth week of lactation. After the sixth week few mothers experience this type of lactational disorder unless they wilfully stop suckling their infants at three or four hourly intervals throughout the day. Various symptoms and signs occur in such a condition but they are not constant and few are pathognomic of inadequate lactation. For instance the mother finds her breasts do not feel tense or firm by the time a feed is due, her milk stops leaking from the nipples and she no longer experiences the "draught". She may also notice that her breasts are not appreciably softer after feeding her infant than they were before the feed. In the initial stage of failing lactation and when the deficiency is not marked symptoms and signs are minimal and may possibly be absent. When they first appear they are more likely to be detected during the latter half of the day than in the morning. If such women are observed for a week or so such signs and symptoms become more apparent in the majority of cases because of progressive diminution in milk yield. As a rule such women are forced to give their infants artificial feeds within a few weeks of the onset of such symptoms.

The symptoms and signs of the second type of inadequate lactation occur after the neonatal period and are due to the mother's milk yield failing to increase sufficiently to meet her infant's growing demands. They usually arise in the third to sixth month of lactation but are occasionally encountered before that stage of lactation. These women are not conscious of any alteration in their ability to lactate. On the contrary they are convinced they have plenty of milk for their infants because their breasts fill well and the milk may even leak from the

nipples between the feeds or while the infant is being suckled. Thus inadequate lactation is not suspected until the infant is weighed and its weight gain is found to be unsatisfactory. A provisional diagnosis of inadequate lactation is made and later is confirmed by the results of test-weighing. Provided the infant is given suitable complementary feeds he will progress satisfactorily, premature weaning being unnecessary in such cases.

SYMPTOMS AND SIGNS OF THE UNDERFED INFANT

While the majority of underfed infants are readily diagnosed by the alteration in their behaviour and stools and by their unsatisfactory weight gain, it is not so generally known that the milk from mothers with a scanty milk yield acts as a gastro-intestinal irritant in some cases (Still, 1927). Confirmation of this statement was obtained when 24 underfed infants were observed for periods ranging from one to sixteen weeks. During that period they were given complementary feeds. Fourteen developed gastro-intestinal symptoms though they were given suitably sized feeds. They became restless, cried excessively, regurgitated and even frequently vomited food and slept for only short periods at a time. The severity and duration of their symptoms varied from case to case but tended to become worse as the mother's milk yield fell. It was found that these infants behaved better after vomiting the breast milk. Nevertheless they did not behave as well as when they were given a complete bottle feed without a preliminary breast milk feed. It was thought that the symptoms might possibly be due to the infant swallowing excessive amounts of air while sucking at an empty breast. To exclude this possibility the infant was given a bottle feed of the suspected breast milk. Such infants developed gastro-intestinal symptoms similar to those experienced when taking milk direct from the breast. It was therefore apparent that the symptoms were not due to air swallowing or sucking at an empty breast. It was concluded that infants who react to their mother's milk in this way should be artificially fed.

The substance or substances in milk which may produce gastro-intestinal disturbances in the breast fed infant have been looked for during the past thirty years. Some investigators noted that such milk had a relatively high chloride content (Sisson and Denis, 1921, Courtney and Brown, 1930), or a high percentage of protein (Carter and Richmond, 1898, Wardlaw and Dart, 1912), or was exceptionally rich in fat (Holt and McIntosh, 1940, Reinhold, 1948). The toxic effect of these substances was not proved. More recently, however, it has been shown that toxic substances can be produced by the abnormal metabolism of fat (Agduhr, 1925 and 1927, Harris and Moore, 1929, Harris and Innes, 1931), and carbohydrate (Kermack, Lambie and Slatter, 1927, Voct-Moller, 1931, Haynes and Weiss, 1940), the former occurring in experimental animals after codliver oil and vitamin

six months was ascertained and recorded in Table I. It is apparent from the figures for the two groups that 59 per cent of infants in group A and 47 per cent in group B were breast fed for six months. The difference between the percentages is not statistically significant. Therefore it seems that the duration of breast feeding does not bear a relationship to the rate at which an infant regains his birth weight.

TO SHOW DAY OF MAXIMUM PHYSIOLOGICAL WEIGHT LOSS IN ENTIRELY BREAST FED
INFANTS BELONGING TO BOTH PRIMIPARA AND MULTIPARA

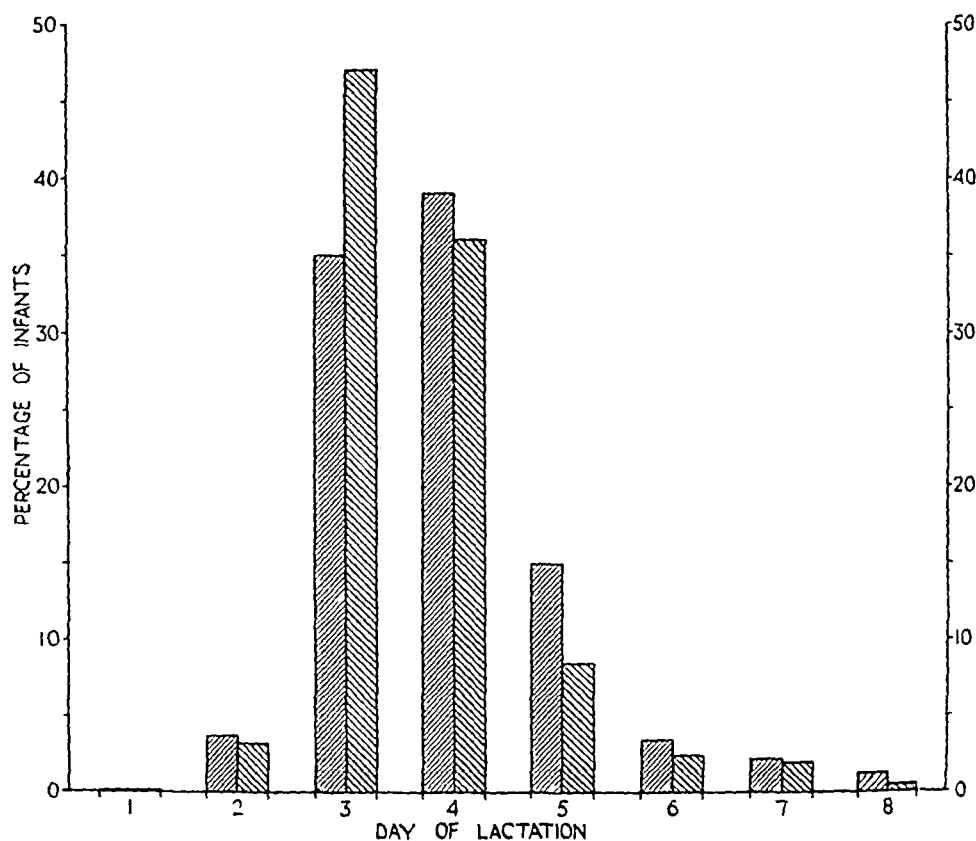


FIG 2

(b) *Routine Weighing after the Tenth Day of Life* —Many mothers like to have their infants weighed at weekly intervals during the first six months of life. This procedure is encouraged at infant welfare centres because the information gained is of great value in assessing the infant's health and correct caloric requirements. When utilising the results it is essential to take into consideration the various factors which affect the infant's weight progress and to know the amount an apparently healthy breast fed infant should weigh when one, two, three, four, five and six months old. These weights can be readily calculated from the figures given in Table II, where the average amount of weight a mature newborn infant gains in four, eight, twelve, sixteen, twenty and twenty-six weeks has been given.

In 67 per cent of cases this weight falls between two levels, namely the "confidence" limits (Table II). The values given in Table II are applicable to any mature infant because its weight progress after

TABLE I

The Duration of Lactation in Women whose Infants (a) Regain their Birth Weight on the Tenth Day of Life, (b) Fail to Regain their Birth Weight on the Tenth Day of Life

Women with Infants	Number of Women	Percentage Breast Feeding in Months						
		1	2	3	4	5	6	
A	116	100	94 0	75 9	70 7	67 2	62 1	59 5
B	211	100	87 2	72 0	60 2	54 5	52 6	47 4

the second week of life is not influenced by its birth weight (Table III). The weight of both male and female infants can be taken from these figures though male infants on the average gain weight slightly faster than female infants (Boyd, 1948). An infant whose weight falls below

TABLE II

The Weight Gain of 247 Breast Fed Infants in the First Six Months of Life

Age in Weeks	Average lb oz	S D oz	Range to Include 67 per cent of Infants	
			lb oz	lb oz
4	1 0	9	0 7	1 9
8	3 1	14	2 3	3 15
12	4 13	18	3 11	4 15
16	6 4	20	5 0	7 8
20	7 8	22	6 2	8 14
26	9 2	25	7 9	10 11

the 67 per cent "confidence" limits must be supervised carefully and the possibility of underfeeding should be considered. Moreover any infant who fails over a period of two weeks to make half the weight progress expected of him (Table III) must be suspected of being underfed.

Test-weighing

Test-weighing of infants over a twenty-four hour period is indicated when they are not gaining weight satisfactorily or under feeding is suspected. From the data obtained the infant's daily milk intake is calculated and compared with the theoretical amount necessary for its weight and age. On the fifth day of life a mature infant requires about $1\frac{1}{2}$ ozs of milk per lb body weight and an infant of this age who obtains less than 1 oz per lb body weight should be given

complementary feeds Similarly, on the eighth day of life the mature infant requires about 2 ozs of milk per lb body weight and those obtaining less than $1\frac{1}{2}$ ozs per lb should be given complementary feeds Infants of fourteen days old or more should have 2 to $2\frac{1}{2}$ ozs of breast milk per lb body weight each day and those failing to obtain this amount usually require complementary feeds, though a few thrive on less than this theoretical amount Exceptions to this rule do occur, for very occasionally infants require more than $2\frac{1}{2}$ ozs per lb body weight before it is contented

TABLE III

The Increase of Weight over Four Week Periods for Infants of Different Birth Weight

Age of Infant in weeks	Mean Weight Gain in Ounces for Infants with a Birth Weight of			All Cases (247 cases)
	lb — lb oz 6 6 15 (67 cases)	lb — lb oz 7 7 15 (112 cases)	lb — lb oz 8 8 15 (68 cases)	
1 4	16 8	16 0	14 0	15 7
5 8	33 9	32 9	31 4	32 7
9 12	29 0	27 4	27 3	27 8
13 16	22 1	22 9	23 7	22 9
17 20	20 9	19 8	20 9	20 4
21 24	16 3	18 4	19 1	18 0

Test weighing sometimes gives misleading information unless the milk remaining in the breast after the infant has fed be taken into account Some women have large amounts of residual milk because they have an abnormality of the nipple or milk sinus which prevents a free flow of milk In others the breast is not emptied because the infant does not suck properly when put to the breast To detect the existence of such difficulties both the breasts and the technique of breast feeding in all cases of suspected inadequate lactation should be carefully checked

THE CHLORIDE AND ELECTRICAL CONDUCTIVITY TESTS

The estimation of either the chloride content or electrical conductivity of breast milk in women suspected of inadequate lactation is of practical value and should be carried out on milk from both breasts when it is not possible to test-weigh the mother's infant (Miller, 1951) The results of these estimations may also indicate the probable duration of lactation (Miller and Jackson, 1951) The method of estimation of both the chloride content and the electrical conductivity and the factors which may influence the results are described by Kermack and Miller (1951a and b)

Milk chloride values which exceed 112 mg per cent in women in the second week of lactation, or 75 mg per cent in women in the third and fourth week of lactation, or 60 mg per cent in women in

the second to sixth month of lactation are suggestive of inadequate lactation. It is important to obtain these values for milk from both breasts before suggesting the diagnosis of inadequate lactation and it has been shown that the higher the values the greater is the chance of the diagnosis being correct. In a few cases high chloride values may be obtained from one breast only. These mothers should be kept under close observation and their infants weighed more frequently in order to obtain sufficient information to give a diagnosis and correct treatment. It is possible, however, to detect by these tests the majority of women whose infants fail to thrive because of inadequate lactation.

Measurement of the electrical conductivity of milk is as simple and informative as the estimation of the chloride content of milk. Conductivity values suggestive of inadequate lactation are those exceeding $270 \times 10^{-5} \text{ ohm}^{-1} \text{ cm}^{-1}$ for women in the second week of lactation, $225 \times 10^{-5} \text{ ohm}^{-1} \text{ cm}^{-1}$ for women in the third and fourth week of lactation, and $210 \times 10^{-5} \text{ ohm}^{-1} \text{ cm}^{-1}$ for women in the second to fifth month of lactation, the values being for milk at 18° . The assessment of the results of the test depends, as in the chloride test, on the height of the values obtained and on whether they are obtained from both breasts, those mothers with only one abnormal breast requiring further investigation before a diagnosis is made.

Routine estimation of the milk chloride or electrical conductivity of women in the second to fourth week of lactation will help the pædiatrician to predict the duration of lactation. For at least 70 per cent of those women who have a milk chloride value of over 100 mg per cent or an electrical conductivity value of over $250 \times 10^{-5} \text{ ohm}^{-1} \text{ cm}^{-1}$ at 18° stop lactating by the time their infants are two months old. Women with lower electrical conductivity values lactate for a longer period.

SUMMARY

Various symptoms and signs of inadequate lactation have been described and an explanation for some of them has been given. Recognition of the different clinical pictures of inadequate lactation was shown to be of value in assessing the probable duration of the lactation.

Routine weighing of an infant, both during and after the first ten days of life was advocated since it was possible to assess adequacy of lactation from the results. Clinical investigations showed that the following findings in an infant's weight chart were highly suggestive of underfeeding: loss of weight after the fifth day of life, failure to gain weight by the eighth day of life, a weight gain over a period of two weeks which was half the expected amount, and an infant with a weight below the lower "confidence limits".

Test-weighing was also found invaluable in investigating infants who were suspected of being underfed. Evidence was collected which

THE VITAMIN B COMPLEX AS A SUPPLEMENT IN INFANT FEEDING

By J A CHALMERS, M D, F R C S, M R C O G

The Royal Infirmary, Worcester

IN spite of Oliver Wendell Holmes' famous dictum that "a pair of substantial mammary glands have the advantage over the two hemispheres of the most learned professor's brain in the art of compounding a nutritive fluid for infants," it is suggested to-day increasingly often that both breast milk and cows' milk may be defective in various vitamins, and consequently all sorts of supplements have been recommended

Clements (1949) considers that human milk should by natural design be the ideal food for the young infant if the condition of the mother is satisfactory, and Jeans and Marriott (1947) state that the milk of a healthy woman contains sufficient amounts of all the nutritional factors necessary except iron, vitamin D and possibly thiamine. With regard to vitamin B complex requirements Crosse (1949) states that little is known, and in a recent paper on infant feeding Evans (1950) makes no reference to vitamin B. Sherman and Smith (1931) state that milk is relatively rich in the heat-stable factors of the vitamin B complex, although Daniels and Brooks (1937) have pointed out that considerable amounts may be lost in sterilisation and even in pasteurisation. On the other hand, Bicknell and Prescott (1946) state that milk is a poor source of vitamin B, and Kasdon and Cornell (1948) describe both human and cows' milk as deficient in the vitamin B complex. Litchfield *et al* (1939) observe that in breast as well as in cows' milk the vitamin B complex, especially thiamine, may be in too low concentration for the optimal wellbeing of the infant, and Macy *et al* (1927) considered that pooled human breast milk from mothers receiving an average American diet was deficient in the vitamin B complex.

During pregnancy, lack of vitamin B complex may lead to foetal malformation (Mussey, 1949) and this may also give rise to anorexia, loss of weight and severe digestive disturbance in the children with lowering of resistance to infection (Kretchmer and Bayandina, 1948), and limitation of growth (Morgan and Barry, 1930). Vitamin B is necessary for carbohydrate metabolism and probably also for protein metabolism (Hess, 1917, Price, 1940) and an adequate supply of thiamine is particularly important where the diet is rich in carbohydrate and poor in fat (Crosse, 1949). In marasmic infants it increases the child's interest in its food (Price, 1940) and in premature children, at least, it helps in the retention of fluids (Litchfield *et al*, 1939).

The mammary gland derives its vitamin B from the blood, and there

is consequently a wide variation in the amount supplied by milk dependent upon the mother's diet (Jeans and Marriott, 1947) This has been stressed by recent figures from Germany (Langendorfer, 1948, Wolfram, 1948, Dean, 1950) showing that post-war malnutrition delayed the return to birth weight of breast-fed infants The effect of maternal diet on the vitamin B intake of the infant is strikingly illustrated in a report from a Pacific island where the prohibition of an alcoholic beverage made with yeast was followed by an acute fulminating type of beri-beri with a 50 per cent mortality among breast-fed infants It was clear that the beverage had been the main supply of thiamine in the maternal diet and when it was allowed once more the infant mortality fell to 7 per cent

With regard to the requirements of the individual factors of the vitamin B complex, Gilder (1950) states that thiamine deficiency leads to anorexia and nausea, but that the effects of deprivation of riboflavin and nicotinamide are still uncertain Clements (1949) observes that significant quantities of thiamine derived from the maternal blood are found in the foetus and that the placenta traps both thiamine and nicotinamide and secretes them to the foetus so that its blood level may be higher than the maternal In addition there may be extensive synthesis of various factors by intestinal bacteria, a process which may be inhibited by altered bacterial flora or such factors as sulphonamide medication or anti-vitamins The administration of isolated members of the vitamin B complex may lead to signs of deficiency of others, and therefore it is better that the main B vitamins be given together (Sydenstricker, 1940) In the first two months an infant requires less thiamine from milk possibly because of its stored thiamine as well as from endogenous synthesis (Slater and Rial, 1942) While the thiamine content of breast milk is probably lower than that of cows' milk there is a greater synthesis in the gut of the breast-fed infant, and in the case of nicotinamide up to 80 per cent of the requirements may be met from this source (Ellinger and Bensch, 1945, Holt *et al*, 1949)

A number of investigations have been undertaken, largely in the United States, to assess the requirements for infants of the various factors of the vitamin B complex Dennett (1929) found a significantly greater weight gain in infants given vitamin B complex for five months as compared with a control group, an observation which was confirmed by Bloxsom (1929) Litchfield *et al* (1939) found an earlier and greater weight gain in children given a yeast extract, and Price (1940) observed that a vitamin B adsorbate significantly increased the growth rate Kasdon and Cornell (1948), using an aqueous preparation from birth in a series of 108 infants, found no difference for three days after birth as compared with 138 controls By the seventh day, however, the test group showed a considerable improvement, the weight gain being 20-50 per cent greater By the tenth day 80 per cent of the test infants had regained or exceeded the birth weight as compared with 59 per cent of the controls, and Litchfield *et al* (1939) gave corresponding

figures of 55 and 8 per cent respectively Taracena del Pinta and Garrido Lestache Cabrera (1949) found that when wheat germ containing an abundance of vitamin B complex was given to 44 infants they gained weekly an average of 84.27 per cent more weight than when the wheat germ was omitted from the diet On the other hand, Elias and Turner (1936) found that brewer's yeast failed to improve the weight gain of infants, and Clements (1949) considered that where the maternal diet was satisfactory a supplement of vitamin B complex should be unnecessary

TABLE I

Content of Various Factors of Vitamin B Complex in Infant Foods (microgrammes)

	Thiamine	Riboflavin	Nicotinamide	Authority
Human milk—100 g or 100 ml	4.8 132 9 15 14 15 20 20 20	16 52 28 62 37 260 1600 5200	260 66 330 183	Garrod <i>et al</i> Slater and Rial Macy, Williams <i>et al</i> Holt <i>et al</i> Bicknell and Prescott Neuweiler
Cow's milk—100 g or 100 ml	19 26 35 40 35 40 40 50 45 75 46	10,000 15,000 150 80 1000 100 300 150	80 90 500 1400 170	Neuweiler Slater and Rial Holt <i>et al</i> Bicknell and Prescott Garrod <i>et al</i> Macy, Williams <i>et al</i>
National dried milk (1 oz)— whole partially skimmed	85 100	330 390	200 280	Scientific Ad viser's Divi sion Ministry of Food

Table I shows the vitamin B complex content of foods commonly used in this country at present for infant feeding In each case the source of the figures has been indicated and it will be seen that there is a very wide range in the figures given by the various authorities This is probably due to regional and national variations in the diet of the milk producers concerned The figures have been converted to microgrammes and the very small inaccuracy due to the unit difference between 100 gm and 100 millilitres has been disregarded

In Table II an attempt has been made to estimate the daily intake of the vitamin B complex factors by young infants Both Ford (1949) and Clements (1949) give a figure of 2½ fluid oz (70 ml) per lb body weight as the optimal daily intake in the breast-fed infant, but in practice it has been found that the average intake has been about 15 oz (425 ml) for a child of about 7 lb On the basis of an average figure from Table I

it is considered that a breast-fed infant will receive 85 mg of thiamine, 170 mg of riboflavin and 850 mg of nicotinamide (Clements (1949) gave figures of 59-112, 180-400 and 430-2152 mg respectively during the first four weeks) When these figures are compared with the theoretical daily requirements it appears that there is a considerable deficiency

TABLE II
*Estimated Daily Intake and Requirements of Vitamin B Complex
Factors (microgrammes)*

	Thiamine	Riboflavin	Nicotinamide
Human milk—15 fl oz (425 ml)	85	170	850
Cows' milk—15 fl oz (425 ml)	170	850	500
National dried milk (1½ oz)—			
whole	128	495	300
partially skimmed	150	585	420
Daily requirements	160 200 (Holt) 400 (Knott)	600 (USNRC)	4000 (Bicknell)
Daily experimental supplement	500	1000	5000

of all these factors in the three types of feeding considered, although Clements (1942) showed that an infant could thrive on a daily thiamine intake of 65 mg. Growth was interfered with if the intake was lower than 50 mg. In view of this theoretical deficiency an experiment has been undertaken in which a vitamin B complex supplement has been given to infants from birth and their progress compared with a similar number of controls whose management was in every respect the same apart from the supplement. The preparation chosen was Elixir

TABLE III
Type of Feeding

Group	Number of Infants	Number Breast Fed	Number Artificially Fed	Percentage Breast Fed	Percentage Artificially Fed
I Rosedene treated	108	84	24	80	20
II Rosedene control	105	83	22	79	21
III Raigmore treated	80	40	40	50	50
IV Raigmore control	87	55	32	63	37
V Total treated	188	124	64	66	34
VI Total control	192	138	54	72	28

Beplex (Wyeth) which corresponded most nearly in its composition to that used by Kasdon and Cornell (1948) in their similar experiment. A daily dose of 4 ml was used which supplied thiamine, 500 mg, riboflavin, 1000 mg, nicotinamide, 5000 mg. This more than covered the theoretical daily requirements of these factors. It was administered in one of the artificial feeds or in an ounce or so of water between feeds in breast-fed infants. Very little difficulty was encountered in administration although on one or two occasions the supplement was vomited. The treated group consisted of 188 infants and the control of 192

infants Of these, 108 treated cases and 105 controls were derived from Rosedene Maternity Hospital and 80 treated cases with 87 controls from Raigmore Hospital, Inverness

Table III shows the type of feeding for each of the four groups and for the total test and control series In all cases considered in this paper the artificial feed used has been partially skimmed National Dried Milk It will be noted that artificial feeding has been used much more frequently at Raigmore Hospital (groups III and IV) than at Rosedene Hospital (groups I and II) The explanation is, firstly, that all tuberculous cases and a majority of unmarried girls in whom breast-feeding was avoided for medical or social reasons were treated at Raigmore Hospital Secondly at Rosedene an attempt has been made to persist with breast-feeding even if it is at first unsatisfactory, whereas

TABLE IV
Stay in Hospital and Weights of Infants (pounds)

Group	Average Stay (days)	Average Birth Weight.	Average at 3 days	Average at 7 days	Average at 9.8 days
I	9.8	7.55	7.17	7.31	7.45
II	9.5	7.9	7.5	7.7	7.9
III	10.3	7.51	7.23	7.42	7.59
IV	10	7.59	7.29	7.48	7.7
V	10	7.53	7.2	7.36	7.44
VI	9.7	7.76	7.49	7.6	7.8

The weight after 9.8 days was calculated by taking the total gain after the 7th day in each group Thence the average gain per child per day after the 7th day was calculated and the average gain in 2.8 days after the 7th This method is accurate enough when the total range of the average stay in hospital is only 0.5 days

at Raigmore Hospital, if adequate lactation is not established early, a readier change is made to an artificial feed This, as will be seen, gives better overall results in the first ten days of life although later it is found that the Rosedene children overtake the others

Table IV shows the average stay in hospital and the weights of infants at birth, at three days, at seven days and at discharge in each group The average stay in hospital was 9.8 days with a range of 9.5-10.3 days All children in hospital less than seven days were excluded from consideration as were all children under 5 lb in weight, and the largest child in the series weighed 9 lb 12 oz at birth It is obvious on studying Table IV that the treated groups I, III and V, show no advantage over the controls, II, IV and VI, and in each instance there is a small difference in favour of the control groups which is not significant

Table V giving the numbers returning to or exceeding their birth weight by the seventh day also shows that there is no advantage for the treated groups This is in direct contradistinction to the findings of Kasdon and Cornell (1948) and Litchfield *et al* (1939) as there is a small advantage for the artificially-fed child in every group

Table VI shows the losses and gains in weight as a percentage of the birth weight. The figure for the average loss on the third day is about half of the $7\frac{1}{2}$ per cent which Langerdorfer (1948) found in his

TABLE V
Numbers Returning to or Exceeding Birth Weight at 7th Day

Group	Breast Fed	Artificially Fed	Total
I	8 (9 per cent)	5 (21 per cent)	13 (12 per cent)
II	20 (23 per cent)	8 (36 per cent)	28 (27 per cent)
III	13 (32.5 per cent)	17 (42.5 per cent)	30 (37.5 per cent)
IV	20 (36 per cent)	15 (47 per cent)	35 (40 per cent)
V	21 (17 per cent)	22 (34 per cent)	43 (23 per cent)
VI	40 (29 per cent)	23 (42.6 per cent)	63 (32 per cent)

post-war series of German women suffering from malnutrition and the figures for the seventh day in this series are considerably lower than the 3.9 per cent deficit which he found on the ninth day. By the date

TABLE VI
Loss or Gain in Weight (Percentage) of Birth Weight

Group	At 3 days	At 7 Days	At 9.8 Days
I	-5.03	-3.18	-1.32
II	-5.07	-2.53	-0.00
III	-3.73	-1.2	+1.65
IV	-3.95	-1.45	+1.45
V	-4.38	-2.26	-0.93
VI	-4.48	-2.06	+0.51

of discharge (9.8 days) in this series, groups III and IV on the average surpassed their birth weight and the deficit for all children was very small indeed and equivalent to 0.23 per cent of the total birth weight.

CONCLUSIONS

In this study of 188 infants to whom a vitamin B complex supplement was administered during the first ten days of life no advantage of weight gain was found at any stage as compared with a control series of 192 infants in whom management was identical apart from the administration of the supplement. Although theoretical considerations would indicate that both human and cows' milk, as well as National Dried Milk, are unlikely to supply enough of the vitamin B complex factors for the needs of the infant, and many feeding experiments have shown greater and more rapid weight gain in new-born infants to whom supplementary vitamin B complex has been administered, the expected advantage in the treated series was not found in this study. The explanation of this is probably in the adequacy of the intake of vitamin B complex in the present maternal diet in the North of Scotland. Yudkin (1950) has stated that in spite of the surplus of many

foodstuffs to be found in the United States, a higher proportion of people there, as compared with Britain, shows obvious nutritional deficiency, and it may well be that the improved growth rate described by Kasdon and Cornell (1948) and many other American authors is a reflection of this fact. Clements (1949) has pointed out that thiamine, derived from the maternal diet, is to some extent stored by the infant towards the end of the uterine life and that consequently demands for thiamine from the mother may be lower during the first two months of life. In premature infants, on the other hand, the storage of thiamine and other vitamin B complex factors has not taken place to the same extent, and the efficiency of synthesis by intestinal bacteria is probably lower so that in these there is still a need for supplementary vitamin B. In the mature infant in this country unless there has been some deficiency in the maternal diet the addition of vitamin B supplements to the feeds in the first days of life appears to offer no advantage.

SUMMARY

1 Theoretical considerations suggest that both breast-fed and artificially-fed infants may suffer from deficient intake of vitamin B complex.

2 A supplement affording, thiamine—500 mg, riboflavin—1000 mg and nicotinamide—5000 mg, has been given to 188 infants which have been compared with a control series of 192 infants whose management in other respects has been identical.

3 No advantage has been found in the treated groups at any stage during the first ten days of life and it is considered that this is due to adequate vitamin B intake by the mother during pregnancy with consequent ample storage by the foetus in the late weeks of pregnancy. It therefore appears that such a supplement is unnecessary.

4 The deficient storage in premature infants suggests that in these, results should be improved by the administration of a vitamin B complex supplement.

I am indebted to Miss Campbell of Rosedene Hospital and Miss Walton of Raigmore Hospital for the care with which they have carried out the additional work involved in this study, to Miss G. Z. Brewster of the Scientific Adviser's Department of the Ministry of Food and Miss Audrey Z. Baker of Vitamins Limited for information about the factors of vitamin B complex, and to Mr G. L. Frewin and Mr Ross Martin for help in the interpretation of the figures obtained.

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OBITUARY

GEORGE LYALL CHIENE

M B, F R C S E

Mr GEORGE LYALL CHIENE died very suddenly at his home in Edinburgh on the evening of 19th November 1951, at the age of 78, though apparently in his usual state of health in the afternoon

The elder son of the late John Chiene, Professor of Surgery in Edinburgh University, he was educated at the Edinburgh Academy, from which he proceeded to Christ's College, Cambridge. Returning to Edinburgh for his medical studies, he graduated M B, C M, in 1897. In the course of the following two years he was house physician to Sir Thomas Grainger Stewart, and house surgeon to Professor Annandale. In the spring of 1900, during the South African War, he went out as Assistant Surgeon in the Edinburgh and East of Scotland Hospital, but in the autumn of the same year this hospital was taken over by the Military Authorities, and the staff returned home, with Mr (now Sir) David Wallace he wrote the Report of that hospital.

In 1901 he became a Fellow of the Royal College of Surgeons of Edinburgh, and was appointed Assistant Surgeon to the Royal Hospital for Sick Children. He was Junior Assistant for a year, and then Senior Assistant for about five years, to his father in the University Department of Surgery, thereafter for many years to held a successful class on Surgery in the Edinburgh School of Medicine. He was elected Assistant Surgeon to Edinburgh Royal Infirmary in 1903, on the same day as Archibald Scot Skirving, succeeded to the charge of wards as full Surgeon in 1922, and retired in 1937 on completion of the statutory fifteen years. He had been President of the Royal Medical Society of Edinburgh, and later of the Medico-Chirurgical Society of Edinburgh.

On the institution of the Territorial Force in 1908 he was appointed Captain in the 2nd Scottish General Hospital, and in the first world war he served in that hospital at Craigleith till in 1918 he was sent as Acting-Major to France. In the second war he emerged from retirement to take charge of the two Royal Infirmary annexes at Corstorphine.

Chiene was recognised as an excellent general surgeon. In 1904 he introduced in Edinburgh the use of "stovaine" as a spinal anaesthetic, and in 1923 he published a popular *Handbook of Surgery*. His special operative procedures included division of both ends of the sterno-mastoid muscle in congenital torticollis, an operation for inguinal hernia, a modification of the approach to the appendix, and an operation for large midline ventral hernia by specially designed lateral incisions for the relief of tension. Chiene was an exceptionally good teacher, and, like his father, taught by word and example the duty and value of a kind and homely approach to patients, often in his case with the use of the Doric, which relieved anxiety and put them at their ease. In his clinical class he introduced every term a debate on a surgical subject, and he was very popular with students because of the excellence of his teaching and his ever-ready and kindly friendship.

He was a good athlete in his younger days. The writer, looking back upon almost seventy years of intimate friendship, remembers playing with him at the end of the eighties in the school cricket XI, and also at centre three-

quarters (there were only three in these days ¹) with Chiene at full back. He remained a good golfer and angler. One of his hobbies was water-colour painting, in which he possessed real skill, and he used his artistic gift successfully in his surgical teaching.

In many ways George Chiene resembled his distinguished father, and, as he grew older, the resemblance in appearance, voice and manner became even closer, and interested and delighted those who had known the Professor. Chiene was in his element at informal dinners, at which he was no mean singer, and at social functions, and he possessed the charm of a simple, genial nature. He is survived by his wife and two sons, to whom we offer our sympathy, and the death of George Chiene will be a very real grief to his widely scattered students and to the diminishing circle of his contemporaries.

NORMAN SCOTT CARMICHAEL

M B , Ch B Ed , F R C P Ed

Dr NORMAN CARMICHAEL, consulting physician to the Royal Edinburgh Hospital for Sick Children, died at his home in 43 Moray Place, on 16th November, at the age of 68.

He was throughout his life an Edinburgh man. Born in Northumberland Street, he was educated at Edinburgh Academy, studied medicine at Edinburgh University and graduated M B , Ch B , in 1905. In his professional path he followed his father in combining general practice with special study of disease in children. He became a Fellow of the Royal College of Physicians of Edinburgh in 1913, when he was already an Assistant Physician at the Children's Hospital. During the 1914-18 European war he went to Salonika with the Edinburgh Hospital, attaining the rank of Major, R A M C , and receiving the Serbian Order of St Sava. On his return home he was appointed in 1920 Physician to the Children's Hospital, and Lecturer in Diseases of Children in the University of Edinburgh. He retired from the hospital service in 1935 on completion of his term of duty. On the outbreak of the second world war in 1939 he again left Edinburgh for military duty at the E M S Hospital at Turnberry, Ayrshire, where he was superintendent and consulting physician. At the close of the war he returned to Edinburgh, resuming his private practice, and also acting for several years as medical superintendent of Leith Hospital. He was also Surgeon-Apothecary to the King at Holyrood Palace, and for many years he was a member of the Royal Company of Archers, King's Bodyguard for Scotland.

His father, Dr James Carmichael, physician to the hospital, his older brother Edward, for some years assistant surgeon, and Norman himself also physician, together made a notable family contribution to the work and teaching of the Edinburgh Children's Hospital. Norman was a sound and popular teacher, and he must have formed the practice and ethical standards of many generations of medical students. Among his hospital colleagues he exerted a powerful influence for good, he never stirred up strife, but when contentious subjects were under discussion, the expression of his views was frank and always courteous, and in all matters his wise, honourable and friendly character gave weight to everything he said. In his last years when the shadows of ill-health and family bereavement fell upon him, he showed great courage and undiminished cheerfulness. By his patients in hospital and private practice and by his medical colleagues his memory will be cherished.

NOTE

At a Quarterly Meeting of the College held on Tuesday, 5th February 1952, the President, Dr W A Alexander, in the Chair, the following were elected Fellows of the College —Charles Mann Fleming, M A, M D GLASG, Walter Henderson, M D EDIN, Henry Edmund Seiler, M D GLASG, Ian Hunter Lockhart Gillies, M D GLASG, William Hugh Galloway, M B EDIN

The following were elected Members of the College —William Boyd, M B EDIN, Irene Parker Rowlands, M R C S, L R C P, F R F P S G, Sidney Stein, B S C CAPE TOWN, F R C S, L R C P, Robert Orton, M D LEEDS, John Norman Armour, M B N Z, Grainger Wilson Reid, M B EDIN, Vincent Daniel Bayliss, B A MADRAS, M B MADRAS, Suraj Prakash, M B PUNJAB, Harold McDonald Forde, M R C S, L R C P, Nathan Gordon, M B WITWATERSRAND, Rajeshwar Prasad, M B PATNA, Balawant Mahadeo Kher, M D BOMB, Leon Albert, M B CAPE TOWN, John Gant, B S C CAPE TOWN, M B CAPE TOWN, Mahadeo Prasad Mehrotra, M D LUCKNOW, Jean Clyne Taylor, M B ABERD, Harry Black, M B N Z, M R A C P, Andrew Cairns Douglas, M B EDIN, Patrick Cushny MacGillivray, M B EDIN, Mohomed Ahmed Botawala, M B BOMB, Suresh Dhireajlal Store, M D BOMB, Robert Stuart Malcolm Douglas Inch, M B EDIN

NEW BOOKS

Syllabus of Human Neoplasms By R M MULLIGAN, M D Pp 317, with 230 illustrations London Henry Kimpton 1951 Price 5s 6d net

At first sight it is a little difficult to see the need for this book, as the subject-matter is dealt with adequately in several of the larger works on tumours. But perhaps the preface indicates its scope of usefulness, where it is stated "such a volume could be of value not only as a text for the medical student, but also as a reference for the intern, the resident, and the practising physician"

Certainly it gives much condensed information about tumours with numerous appropriate illustrations. But some of the statements are not very helpful, e.g. on page 11. The term malignancy is used "when the constituent cells show lack of uniformity, relatively little resemblance to the cells from which they spring invasion and metastasis". But on page 12 it is stated "although a neoplasm may be benign by slow growth and uniform histologic characteristics, position may make it malignant, as in the case of a huge retroperitoneal lipoma by endangering vital structures"

In other places, conditions not neoplastic are described without it being clear as to their relation, if any, to neoplastic processes, e.g. under the general heading of "Neoplasms of Mesenchymal Origin", subheading "Hæmopoietic Diseases of Uncertain Status", there appear such things as Infectious Mononucleosis, Hodgkins' Disease, Cerebrosidosis (Gaucher's disease), and allied states. Again under Thyroid page 245, there are detailed descriptions of different forms of goitre but no clear indications of their relationships, if any, with thyroid neoplasms.

There are numerous references to each chapter, the great majority being to American literature only.

A few minor, and obvious, misprints were noted.

The book is well produced and, in spite of the criticisms above, well worth perusal.

Human Blood Groups and Inheritance By S D LAWLER, M D, and L J LAWLER, B SC Pp viii+85, with 6 figures Paper covered London Heinemann 1952 Price 3s 6d

Most of us who practise medicine find it difficult enough to keep up with developments in our own field without having to note progress in other departments, especially one like the study of blood groups which advances so rapidly

This small monograph written by experts belongs to a series designed for the intelligent layman and therefore well suited to the uninitiated medical man It ranges from Empedocles (*circa* 500 B C) right up to the present, showing the development of our knowledge of the blood groups To those of us brought up on the A, B, AB, and O system and the rhesus factor it is a surprise to learn that there are now nine different systems, one of them less than a year old The book is clearly written, not too highly technical and well worth the attention of the casual medical reader

The British Journal of Tuberculosis and Diseases of the Chest Edited by P ELLMAN, F R C P Pp 80, illustrated London Bailliere, Tindall & Cox Price quarterly 8s Annual subscription 30s

With the January number of this journal this publication enters its forty-sixth year in an enlarged and extended form The editorial board has been enlarged by the inclusion of representatives of Australia, New Zealand, South Africa and Canada

This successful journal devoted primarily to tuberculosis also covers diseases of the chest and carries a series of excellent papers We congratulate our contemporary and wish it continuing success

The Quiet Art By ROBERT COOPE, M D, B SC, F R C P Pp vi+284 Edinburgh E & S Livingstone 1950 Price 12s 6d net

Dr Coope, a leading Liverpool physician, offers to the profession a remarkable collection, chiefly from the writings of medical men of all ages Some are long, many are brief—sometimes only a sentence or so They cover a wide range of topics and all aspects of medicine, reflecting the varied interests of the practitioner Many are light-hearted and amusing, others epitomise wide experience and profound advice Open the book where you will and your interest is at once aroused

The Specialities in General Practice Edited by RUSSELL L CECIL, M D Pp vii+818, with 470 figures London W B Saunders 1951 Price 72s 6d net

Let not the above title, by virtue of its American parentage, mislead the general practitioner of this country, for, in a less vast country, his field of operation is limited in comparison with the American counterpart Cecil, himself, states in the editorial that the book's fullest use will be found where "early consultation with a specialist is not feasible" As in his *Textbook of Medicine*, the book comprises of chapters subscribed by varying American specialists, encompassing the bulk of problems occurring in general practice

With regard to clarity of text and illustrations, the chapters devoted to orthopaedics and minor surgery are excellent It is unfortunate, in these chapters, and those on gynaecology and obstetrics that 60 per cent of procedures require hospitalisation, and that they are therefore outwith the scope of the British practitioner

Digests of diagnoses and treatment in ophthalmology, pediatrics and urology deserve special mention, and find no British counterpart in such compressed yet lucid form It is inevitable that some of the opinions expressed will excite opposition in this country

Although expensive, this textbook surveys such a wide and useful field, that its constant daily use will repay its outlay

NEW EDITIONS

Human Anatomy and Physiology By N D MILLARD and B G KING Third Edition Pp 590 Philadelphia and London W B Saunders Company 1951 Price 22s

Experience of previous editions has helped the authors to produce in this book an excellent survey of the main processes of the body in which simple explanations of the physiology follow after covering the relevant anatomy and histology in each section

Clarity has also been helped by numerous good diagrams, many useful tables and by omitting the tedious description of animal experiments

It can be recommended as an introduction for medical students or as a textbook for courses in subjects allied to medicine

A Textbook of Pathology By ROBERT ALLAN MOORE Second Edition Pp viii+1048, with 501 illustrations London W B Saunders Company 1951 Price 63s net

This edition appears six years after the first and is characterised by much revision and expansion of the original text The new material relates among other subjects to the metabolism of enzymes, infectious conditions, diseases of the aged, bony dystrophies, effect of atomic explosion and vitamins Such primarily long chapters as those on viral, alimentary and neoplastic conditions have been subdivided, while nephritic, collagenous and demyelinating diseases are now each dealt with in individual chapters Many abnormalities such as lower nephron disease, heart failure and adrenal insufficiency, moreover, are modernised on the basis of newly acquired knowledge As before, the text is supported by numerous well reproduced illustrations and selected references to the literature and is appended by an ample index The new product as a whole thus constitutes a comprehensive, up to date and stimulating treatise in human and experimental pathology with an enhanced appeal to both student and specialist

Diathermy, Short wave Therapy, Inductotherapy, Long-wave Therapy By WILLIAM BEAUMONT, M R C S, L R C P Second Edition Pp viii+230, with 114 illustrations London H K Lewis 1952 Price 21s net

Does the profession get the optimum value from diathermy? The principles of diathermy and the apparatus are very clearly described in this book After a short discussion on the risks and dangers a detailed and very clear description is given of the many uses of diathermy This is a most useful book for the practitioner who wants to know the scope of diathermy and also its limitations This can also be used as a textbook for the student preparing to use diathermy in practice An extensive glossary of technical terms comprises the terminal chapter

Recent Advances in Clinical Pathology Edited by S C DYKE, D M, F R C P Second Edition Pp vii+575, with 37 plates and 36 figures London J & A Churchill 1951 Price 40s

As in the first edition this book is divided into four sections—bacteriology, biochemistry, hæmatology and histology—and all the newer methods used in laboratory diagnosis are fully described and their value discussed In all the sections much is found of great interest to the clinician as well as to the clinical pathologist, as for example the chapters on the Rh factor and liver function tests The plates and figures are beautifully reproduced and clear and the indexing good This new edition should prove of great value to clinician and laboratory worker alike

Clinical Laboratory Diagnosis By SAMUEL A. LEVINSON and ROBERT P. MACFATE
Fourth Edition Pp 1146, with 221 illustrations and 13 plates, 10 in colour
London Henry Kimpton 1951 Price 84s

The fourth edition of this book continues the American tradition in works of clinical pathology. This compendium provides methodological detail and interpretation covering clinical biochemistry, hæmatology, immunology, serology, bacteriology, tropical diseases, milk and water analysis, histological technique and toxicology. The authors say their objective is, "To present to the student, intern practising physician and medical technology, a suitable review of clinical laboratory diagnosis." Whatever may be the situation in America it is difficult to imagine this objective being realised in this country, the needs of these groups are so varied that one volume is unlikely to serve each adequately. The medical technologist will benefit most from possession of the book especially if he is working in a general laboratory. Much of the material is excellent and the details of method are lucid. There are, however, a few strange omissions, e.g. no mention is made of vitamin B₁₂ in relation to pernicious anæmia and no method is described for the estimation of urinary 17-keto-steroids, although a reference to urinary biotin determination is given.

BOOKS RECEIVED

- ANSON, BARRY J., M.A., PH.D (MED. SC.), and MADDOCK, WALTER G., M.S., M.D., F.A.C.S. *Callander's Surgical Anatomy* Third Edition
(W. B. Saunders Company, London) 70s
- BROCK, R. C., M.S., F.R.C.S., F.A.C.S. Astley Cooper
(E. & S. Livingstone Ltd., Edinburgh) 20s net
- CLARK, W. E. LE GROS, F.R.S. *The Tissues of the Body* Third Edition
(The Clarendon Press, Oxford) 30s net
- CLARKE, BRICE R., M.D. *Causes and Prevention of Tuberculosis*
(E. & S. Livingstone Ltd., Edinburgh) 32s 6d net
- DALAND, GENEVA A., B.S. Edited by HAM, THOMAS HALE, M.D. *A Colour Atlas of Morphologic Hematology*
(Harvard University Press, Cambridge, Mass.) \$5.00 (32s 6d) net
- ELLMANN, PHILIP, M.D., F.R.C.P. *Essentials in Diseases of the Chest for Students and Practitioners*
(Oxford University Press, London) 30s net
- Introduction by GUTTMACHER, ALAN F., M.D. *Hippocrates on Intercourse and Pregnancy*
(Henry Schuman Inc., U.S.A. (New York)) \$2.50
- HILL, HARRY, F.R.S.N.I., A.M.I.S.E., F.S.I.A. *Clean Milk*
(H. K. Lewis & Co. Ltd., London) 7s 6d net
- Edited by ILLINGWORTH, C. F. W., C.B.E., M.D., CH.M., F.R.C.S.E., F.R.F.P.S. (GLAS.) *Textbook of Surgical Treatment, Including Operative Surgery* Fourth Edition
(E. & S. Livingstone Ltd., Edinburgh) 45s net
- MACKEY, HERBERT O., F.R.C.S.I., L.R.C.P.I., D.P.H. (DUB.) *A Handbook of Diseases of the Skin*
(C. J. Fallon Ltd., Dublin) 7s 6d net
- MUIR, ERNEST, C.M.G., C.I.E., M.D., F.R.C.S. (EDIN.) *Manual of Leprosy Supplement to the First Edition* (E. & S. Livingstone Ltd., Edinburgh) 2s 6d net
- ROBERTS, FFRANGCON, M.D. *The Cost of Health* (Turnstile Press, London) 16s net
- SINGER, CHARLES. *New Worlds and Old*
(Wm. Heinemann, Medical Books Ltd., London) 15s net
- TAIT, EDWIN FORBES, M.D., PH.D. *Textbook of Refraction*
(W. B. Saunders Company, London) 40s
- TATLOW, W. F. TISSINGTON, M.D., M.R.C.P. (LOND.), ARDIS, J. AMOR, M.B., CH.B., D.P.M. (BRIST. & LOND.), and BICKFORD, J. A. R., M.R.C.S., L.R.C.P., D.P.M. (BRIST.) *A Synopsis of Neurology*
(John Wright & Sons, Ltd., Bristol) 30s Post 11d
- WALKER, G. F. M.D., F.R.F.P.S.G., D.C.H., M.R.C.P. *The Asthmatic Child* Second Edition
(John Wright & Sons, Ltd., Bristol) 2s 6d Post 2d
- By Members of the Staff of Lahey Clinic, Boston. *Surgical Practice of the Lahey Clinic*
(W. B. Saunders Company, London) 75s
- WECHSLER, ISRAEL S., M.D. *A Textbook of Clinical Neurology* Seventh Edition
(W. B. Saunders Company, London) 47s 6d

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ENDOGENOUS LIPID PNEUMONIA

B. H. G. MORGAN, B.Sc., M.B., Ch.B.

Lecturer in Pathology, University of St Andrews, Royal Infirmary, Dundee

THE lipids causing pulmonary disease are not so often exogenous as is commonly thought. It is now well known that among the lipids which may reach the lungs by the air passages, the inhaled or exogenous lipids, there are many, whether animal, vegetable or mineral, which lead to chronic fibrosing lesions of the lung [Graef, 1939 (pathological), Freiman *et al*, 1940 (pathological and clinical), Sodeman and Stuart, 1946 (clinical), Schneider, 1949 (clinical), Proudfit *et al*, 1950, and Harter, 1950 (industrial cases), Losner *et al*, 1950 (diagnostic points), Berg and Burford, 1950 (surgical viewpoints)] Part of the purpose of this paper is to point out that lipids associated with fibrotic pulmonary disease are in many, and probably most cases, not inhaled lipids but actually *endogenous*.

TABLE I
LIPID PNEUMONIA

<i>Exogenous</i>	<i>Endogenous</i>
(Oil aspiration pneumonia)	(Retention granuloma)
(1) Animal oil	(1) Bronchial narrowing
(2) Vegetable oil	(2) Bronchiolar narrowing
(3) Mineral oil	

Although it has been known for long that lipid-containing phagocytes are occasionally to be found in chronic inflammations of lung, and particularly in those associated with bronchial obstruction, it remained for the workers at the Massachusetts General Hospital (Robbins and Sniffen, 1949, Waddell, Sniffen and Sweet, 1949) to emphasise the lipid-containing nature of the widespread proliferative lesion that commonly follows obstruction of the smaller air passages. In this department pathological observations similar to those of Sniffen have been made independently on a series of pneumonectomy specimens.

This series consisted of eight pneumonectomies—five with bronchial neoplasm (one adenoma), one with late unresolved pneumonia, and

Abstracted from a paper read at a meeting of the Tuberculosis Society of Scotland held in Dundee on 15th June 1951

two with unresolved pneumonia and chronic abscess formation—and one necropsy specimen of carcinoma. In five there was lipid pneumonia obvious to the naked eye (see Table II), and all showed the histological changes illustrated by Sniffen in 1949. These are quite distinct from the pulmonary changes seen in the generalised lipidoses (Oswald and Parkinson, 1949, Thannhauser, 1950) and the latter are not further discussed here.

TABLE II

Case Reference	Anatomic Diagnosis	Other Lesions	Lipid Changes
1 101/34 (necropsy)	Squam carcinoma	No gross bronchiectasis, L L L	Obvious to naked eye
2 314/4/50	Squam carcinoma	Unresolved pneumonia, fibrotic stage, L L L	Found microscopically
3 32176/50	Anaplastic carcinoma	Areas of fibrosis, R L L	Found microscopically
4 32244/50	Anaplastic adeno carcinoma	Unresolved pneumonia and early bronchiec tasis of R M L	Found microscopically
5 85/51	Squam carcinoma	Bronchiectasis, R M L and R L L	Obvious to naked eye
6 1697/51	Bronchial adenoma, invasive	Areas bronchiectasis and unresolved pneu monia, L L L	Obvious to naked eye
7 485/51	Unresolved pneumonia, late fibrotic stage, L L L		Found microscopically
8 528/51	Unresolved pneumonia, fibrotic stage, R U L	Several small chronic abscess cavities	Obvious to naked eye
9 1448/51	Unresolved pneumonia, late fibrotic stage, R M L	Two fairly large chronic abscess cavities	Obvious to naked eye

To gross examination, the affected lung tissue appears grey and fibrotic, with thickening of the adjacent pleura and interlobular septa, and in each case an entire lobe or major segment is involved. The endogenous lipid, when abundant, is seen as a pale yellow opaque speckling, often staphyloid, clustering especially towards the periphery of the lobe and also of each affected lobule.

The main histological feature of endogenous lipid pneumonia in this series is a low grade inflammation either secondary to an obstruction of the major bronchi, often with a bronchiectatic picture, or apparently confined to the bronchioles. Associated with both types is a distension of the distal alveoli by masses of lipophages, forming very obvious lagoons or backwaters. In these a peculiar feature is the almost complete absence of inflammatory cells among the large lipophages (which are recognisable as foam cells in ordinary paraffin sections). Lipid material, both intra- and extra-cellular, is also present in quantity in the thickened proliferated stroma which separates these congeries of lipid-filled, but neither inflamed nor fibrosed, alveoli (the lagoons). In other parts the alveolar walls may show fibrous thickening, going on to carnification. Lymphoid proliferation is also common. The lipid itself occurs in two intermingled forms, as small strongly sudanophilic

crimson globules and as doubly refractile crystals which are only faintly sudanophilic. The histochemical reaction of Schultz (Lillie, 1948), which is given possibly by all unsaturated sterols (Yoffey and Baxter, 1949, Pearse, 1951), as well as ordinary chemical analysis of the lung tissue, show that the lipid is largely of sterol nature (cholesterol and cholesterol esters). The possibility that these sterols when present in the stroma may, like paraffin oil, be irritant and lead to fibrous proliferation has also been suggested by Sniffen.

CHEMICAL INVESTIGATION OF LUNGS (Table III)

The lipids present were estimated in a sample of normal unfixed lung and in two samples of abnormal lung, fixed in 10 per cent formal-saline, showing fibrosis and visible lipid formation. The fixed material was thoroughly washed and dried between sheets of blotting paper. All these samples, weighing from 60 to 146 g, were dried *in vacuo* at 100° C to constant weight. The dry material was extracted in a Soxhlet apparatus first with ether and then with alcohol. A sample of the dried lipid was used for estimation of free and total cholesterol by the method of Schoenheimer and Sperry (1934).

The results show that the water content of the normal and abnormal lungs is of the same order, but that there is a marked difference in the total lipid present. Cholesterol and cholesterol esters together form the main constituent of the abnormal lipid. The total cholesterol also forms a much higher percentage of the lipid in abnormal than in normal lung tissue, the increase being mainly in the cholesterol ester fraction.

TABLE III

Analyses of Normal and Diseased Lung Tissue

	Normal	Abnormal	
		(1) Reference 528/51	(2) Reference 85/51
Water content per cent	84.7	83.5	85.0
Total lipid as per cent wet weight	0.9	3.7	2.2
Total lipid as per cent dry weight	5.8	21.5	14.9
Total cholesterol as per cent dry weight	1.2	12.4	10.8
Free cholesterol as per cent dry weight	1.2	1.8	2.3
Ester cholesterol (by difference)	0	10.6	8.5
Total cholesterol as per cent lipid	21.3	57.7	72.3
Ester cholesterol as per cent total cholesterol	0	55.0	78.0

NOTE.—Of the two abnormal lobes from which samples were taken for analysis, (1) an unresolved pneumonia, showed no obvious bronchial obstruction, while (2) was distal to a bronchial carcinoma.

It is a familiar fact that low grade inflammatory processes of some standing may contain large amounts of sterol, actinomycotic lesions also frequently show the presence of lipophages. The histological

picture in the lungs in this series certainly indicates that the inflammatory changes are of low grade, but proof of a fungal element has not been established. The irritant effect of the presence of sterols in stromal tissues is known in general pathology, and the association of the interstitial lipid with fibrotic changes in these lungs suggests that the sterols (or possibly other lipids) have been exerting some such irritant effect. It is still an unexplained problem why lipophages congregate in, and come to distend, groups of alveoli in which inflammatory cells are conspicuously absent.

The source of the lipids is probably the inflammatory exudate, since the lipid is seen to appear first in large phagocytic cells which surround the purulent exudate in the air passages, these cells may be numerous enough to form an obvious zone. Similar lipophages are scattered singly in the alveolar exudate. They may well all have taken origin from histiocytes, which Thannhauser (1947) believes are capable of forming various lipids, including cholesterol.

A point of clinical importance lies in the recent advocacy of the examination of sputum, lung puncture, or biopsy material in cases of chronic localised pulmonary disease. It has been suggested (Losner *et al*, 1950) that if lipid is found on such examinations then the condition is an exogenous lipid pneumonia and not a carcinoma. In striking contrast to this, Reingold *et al* (1950) report that in a series of 60 cases of bronchial carcinoma, 16 showed in addition what was thought to be an inhalation oil pneumonia (exogenous lipid pneumonia). It would appear that these writers were apparently unaware of *endogenous* lipid pneumonia and its frequent occurrence as the result of a bronchial obstruction. The finding of even endogenous lipid is not, however, a proof of bronchial obstruction, and I can confirm Sniffen's original observation, and the recent work of Ashe *et al* (1951), that an endogenous lipid pneumonia can occur in the absence of obstruction of major bronchi. The paper by Navasquez *et al* (1951) on the endogenous form of lipid pneumonia is incomplete, since they have described the lesion merely in relation to carcinoma of bronchus and apparently have not observed the other types of endogenous lipid pneumonia, or seen the work of the American pathologists on this subject. One practical implication of the recognition of endogenous lipid pneumonia is that the finding of lipid in sputum or in aspirated lung material neither excludes nor specifically indicates the presence of carcinoma.

SUMMARY

Lipid pneumonia may be due to the inhalation of various exogenous lipids (chronic lipid pneumonitis, oil aspiration pneumonia, pulmonary paraffinoma, etc). It is probably true to say, however, that the commonest form of lipid pneumonia is due to the presence of *endogenous* lipids. These occur focally in lungs the seat of chronic obstructive lesions of the bronchi or of the bronchioles when the accompanying inflammation is of low grade. It seems clear that these

lipids in their turn lead to fibrotic changes, and it is therefore probable that many of the cases reported in the past as due to exogenous lipids were in fact of endogenous type. These findings are of importance to both clinicians and pathologists in the differential diagnosis of chronic localised pulmonary disease.

I am indebted to Professor A. C. Lendrum for his advice in this study, to Mr Martin Fallon and Dr D. G. McIntosh for the pneumonectomy specimens and clinical details, and to Dr R. P. Cook for advice and facilities in the estimation of lipid.

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A STUDENT'S NOTEBOOK OF JAMES SYME'S CLASS OF CLINICAL SURGERY IN 1861-62

Kept by WILLIAM McNEIL, M D Ed 1864 with extracts and comments
by CHARLES McNEIL, M D Ed, F R C P Ed & Lond

IN 1861 James Syme, Professor of Clinical Surgery in the University of Edinburgh, was at the height of his power, reputation and influence. His clinical lectures began on 1st May 1861 and continued twice weekly until 3rd February 1862, interrupted by summer vacation from 26th July till 6th November 1861, in this course, 163 patients, young and old, were examined, diagnosed and treated and demonstrated by Syme to his class of students, then in their second year, and studying anatomy and dissection at the same time one of these students was William McNeil of Stranraer, and his notebook with the title "Cases of Clinical Surgery by Professor Syme 1861—" is the subject of this communication.

The notes are fuller than those usually made by students. They go beyond the details of the diagnosis and treatment of cases. They are a lively narrative of the whole scene, giving touches of personal description of the patients, and their demeanour under stress and pain, dialogues between surgeon and patient, many anecdotes and stories told by Syme and drawn largely from his own vast experience, and the essence of the subject—the demonstration of patients by a great surgeon to his students and the exposition of his principles and practice.

Some extracts from this notebook are presented by the writer of this communication, who is the son of the Edinburgh medical student of 1861. They show something of what went on in a surgical hospital ninety years ago. They bring back to life the acts and words of an outstanding surgeon of his generation, also the words and reactions of his patients and the admiring audience of his students. They may thus serve to justify and preserve the reputation of Syme as a great teacher.

THE PATIENTS PERSONAL TOUCHES

A few extracts show one feature of the notebook, its touches of personal description of the patients, they are little trivial facts and yet they complete and humanise the surgical record and bring the scene to life.

"1st May 1861 Case 6th A little girl from Wales, aged 8, was brought in by Dr Annandale to-day. She seemed in the very highest spirits, was carrying a large doll very gaily dressed, and laughed immoderately at the round of applause with which the students greeted her appearance. For more than a year she had been in failing health in consequence of a large tumour which had grown to the lower jaw under her right ear."

" 21st November 1861 Case 18th A young man from Fife was first brought in to-day He had crossed the Firth this morning to obtain relief from Pr Syme, having swallowed a copper coin yesterday

It seems he is the son of a wealthy German banker in Gottenburg who had sent him to Fife to learn farming A very intelligent young man "

" 27th May 1861 Case 28th A man, aet 40, came in next, and on entering very gracefully saluted the Pr From his style of salutation I should think he is a soldier His arm was bandaged " After describing the condition with Syme's remarks, the note concludes " the man on leaving, again, most politely bowed to the Professor "

" 3rd June 1861 Case 39th A child 4 years of age was next carried into the room by his Father, a small farmer in Berwickshire who had come that morning into Edinburgh a distance of 50 miles to see Professor Syme " Examination showed the case to be Hydrocele of the cord and operation was at once carried out, and the note ends " the little fellow—very beautiful, like all previous children receiving chloroform, was quite frightened and cried out piteously for his mamma, till the chloroform established its sway "

" 19th July 1861 Case 73rd A poor little rascal was next introduced with his arm in a sling Very wistfully he looked at Pr Syme as he was lifted by Dr Annandale and placed on the chair beside him On Pr Syme asking him how his arm had been hurt, he said, ' I fell, Sir, aff anither boy's back ' "

SYME'S STORIES

Syme in his teaching made great use of stories " to point a moral and adorn a tale "—stories drawn from his own and others' experience In the 1861-62 notebook of his clinical lectures it is fortunate that these stories are carefully and fully recorded, in themselves they are often dramatic, sometimes melodramatic, but closely relevant to and a powerful enforcement of points and principles in the case or subject under discussion Two examples are given

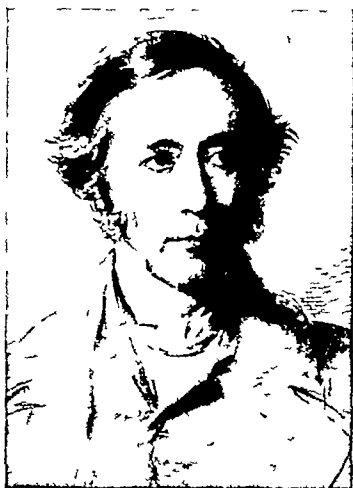
Gluteal Aneurism and Ligature of the Internal Iliac Artery—1861 was a notable year for Syme in that two cases of gluteal aneurism presented themselves at the Infirmary within a few days of one another, and both were successfully treated by ligature of the internal iliac artery (Joseph Lister coming from Glasgow to assist at the second operation) Syme published his account of the cases in 1862 in his usual short, concise and condensed narrative, but to his students in his clinical lectures he expanded himself widely over the whole subject of aneurism, its methods of treatment, with particular application to the two present cases of gluteal aneurism, and the notebook contains a full account of the proceedings in the surgical amphitheatre, the appearance of the two cases, and their operations amid great professional interest, their progress and final cure

" 16th May 1861 Case 19th A man about 25 years of age was next introduced, a strong athletic fine-looking fellow Since the beginning of January he had felt a swelling over the gluteal region. On his stripping, this looked as large as a duck's egg When Pr. Syme put his finger on the tip of the rounded swelling, the pulsation was quite perceptible not only on the tip, but also equally over all the swollen part This at once rendered the nature of the swelling apparent, viz an aneurism of the gluteal artery " Syme then entered on a long exposition of aneurisms in general, citing authorities and his own views and experience as to their treatment, and the lecture ended thus in the words of the notebook —" Pr Syme told another story of a farmer in Ayrshire, who having aneurism of the gluteal artery, and being very much distressed with pain sent for two qualified practitioners in his neighbourhood, who pronounced it to be an abscess and would at once proceeded to open into the supposed abscess, had not they imagined that it was not quite fit for such an operation They left, promising to be back next day and open into it That night a person, who went about the country and acted as Doctor Bone-Setter, happened to arrive at the Farmer's house and was allowed to stay all night At the usual time of retiring to rest, he was shown to bed and slept soundly till awakened early next morning before daylight, to come and let out the farmer's abscess which had become very painful In the grey light of that dark winter morning, he made the desired incision, but was surprised to find that, instead of a yellowish stream of matter as he expected, a dark purple stream was flowing rapidly from the wound Alarmed at the appearance, they sent for the two medical gentlemen already alluded to, who saw at once what had happened In vain they attempted to stop the flow of blood, which continued for two days till the Farmer died These Doctors then lodged a criminal information against the Quack who was apprehended and lodged in prison on a charge of culpable homicide The Lord Advocate referred the case to Pr Syme, who hearing all the facts thought that no criminal charge could be substantiated against the Bone-Setter, as he had acted at the wish of the Farmer, and in the same way as the two qualified practitioners themselves intended to act next day The Quack was thus saved "

In the case before us, Pr Syme intended to tie the internal iliac artery

" May 29th The operation above referred to was performed to-day The theatre crowded to the roof A great many of the Edinburgh Surgeons and Physicians present Pr Syme cool and decided as usual The Superficial (External) Iliac artery was cut in making the incision and tied, incision made very free—as soon as the operation which took about 20 minutes was over it was found that the aneurism was reduced to a third of the former size "

After further notes on the progress of the case the final report is —
 " 19th July Case 19 was brought in to-day that we might see him before going home (John Smith, Shoemaker, Carluke) He is stiff a



JAMES SYME



WILLIAM MCNEIL

little still, but improving fast I saw him on the North Bridge at 3 o'clock "

Internal Hæmorrhoids —Another telling story is given when Syme was explaining and carrying out the surgical treatment of hæmorrhoids external and internal "The best remedy for such a state of matters was to remove the internal hæmorrhoids by ligature while the external, if any, should be removed by the knife " This he did in this case (71) In tying the ligatures he said "You must tie the legatures *as tightly as possible*, if you do not, your patient will suffer intolerable agony " He told us a story of a Dr N— of Inverness, who some 29 years ago had come to him in Edinburgh, seeking relief from pain endured from Internal Hæmorrhoids He was a strong powerful man, and willingly submitted to the operation of having them tied At that time it was customary to tie them so tightly as just to strangle them Well, he had not been long operated on, when the pain became intolerable Pr Syme was sent for, and when he came found Dr N— shouting out in the wildest manner Indeed so fearful were his cries that he alarmed the whole people in the neighbourhood of the street in which he sojourned during his stay Well, to relieve him, he (Pr S) administered an opiate, and in course of time he came round, and went back to a large and extensive practice which he conducted with much ability After a time his old complaint returned, but so dreadful had been his sufferings on the former occasion that it was only when he could no longer sit with comfort that he was forced to come back to Edinburgh for relief And when he did come, the strong vigorous manly fellow was reduced to a shadow Between the period which had elapsed from his first to his second coming to Edinburgh, Professor Syme had discovered that the tighter these hæmorrhoids were ligatured the less pain was suffered, in fact he had found out the proper method of treating such growths Dr N— got the benefit of this improved method of treatment On the second occasion he suffered comparatively little, and returned to Inverness greatly improved in health, and continued up till his death to practice without a return of the complaint "

REACTIONS TO PAIN DURING SURGICAL OPERATIONS

In 1861 chloroform was being used more and more often in minor and in nearly all major operations But in quite a large number of the smaller operations, no anæsthetic was used and patients had to endure severe pain, and surgeon and students were witnesses of their sufferings The bearing and behaviour of patients, and the reactions of the non-patients under these conditions, are often mentioned in the notes Three examples are given

(1) "21st May 1861 Case 25th A man about 60 was brought in to-day suffering from hydrocele The looks of the old fellow as he undressed were quite amusing When Pr Syme approached him with the trocar, the looks of dismay with which the patient regarded it were

irresistible Pr Syme did not give him many seconds to think he at once introduced the instrument through which a copious stream of water flowed When the fluid was drawn off Pr Syme with a syringe injected a quantity of Iodine into the bag to produce irritation The moment the Iodine was introduced, the old fellow shouted at the top of his voice and danced about as if mad Pr Syme said it was not pain that caused him to cry out, Iodine never produced pain, it was just the peculiarity of the patient, and *surprise* ”

(2) “ 15th July 1861 Case 69 A young man, aet 23, was next brought in, his leg (right) bent at knee and just able to touch the ground with the tip of his toes On examining the leg, Pr Syme found that the disease was confined to the Tarsus, and for 3 years the tarsus had continued thick and unyielding, but there was no tendency to suppurate Pr Syme said we would all recollect the treatment for cases of swelling that felt hard on examination and had no tendency to suppurate—the Actual Cautery He then turned to the young man and said ‘I must make an opening into this Can you stand the operation without taking chloroform?’ The young man then asked the Pr if it would be very painful The Pr said ‘Oh, not very’ ‘Very well,’ said the young man, ‘I will try it’, little thinking of the very painful nature of the ordeal he was about to undergo The Dressers gathered round him, and the Pr told him not to look McLean brought in the red-hot iron, which was immediately applied As soon as the poor fellow felt the hot iron, he cried out ‘Oh! I wish I had taken chloroform’ He struggled in vain The Dressers held on remorselessly, and Pr S applied the hot iron until the smoke ascended to the roof of the house When it was over, Pr S asked him ‘how he liked it’ ‘Ah! Sir, it was very sair’ ‘Not very,’ said the Pr ‘Deed, it was, Sir,’ said the victim as he hobbled away Pr S remarked that it was pardonable to understate to a Patient the nature of the pain that might require to be inflicted at any time in an operation ”

(3) “ 21st Nov 1861 Case 12 was that of an old surly-looking fellow, who was brought in, suffering from a very rare disease north of the Tweed, viz Chimney Sweeper’s Cancer on Scrotum When asked by Pr Syme if he had ever been South the Tweed, he said in a very surly tone, ‘Aye, I hae been in Perth’ ‘Had he ever swept chimneys?’ ‘Na!’ When asked if he would take chloroform or not, he made no reply Pr Syme with a pair of scissors at once cut out the cancer which was situated on the most dependent part of the scrotum The shouts of the old fellow were terrific Pr Syme, after he had completed the tying of the vessel cut, questioned him concerning the period of its growth, and got for a reply ‘Hoo the devil can I answer ony questions just noo?’ This created a very hearty laugh among the students, which did not improve the temper of the patient He left the theatre uttering imprecations on Pr Syme and all concerned ”

These extracts and other like incidents in the notes suggests a charge of callousness in surgeon and students Without discussion of this,

two quotations from "Rab & his Friends" are apposite "In them" (medical students), "pity as an *emotion* ending in itself or at best in tears and long-breath, lessens—while pity, as a *motive*, is quickened and gains power and purpose" The second quotation is after the operation on Ailie by Syme—"The surgeon dressed her, and spoke to her in his own short kind way, *pitying her through his eyes*"

"A GOOD SURGEON" QUALIFICATIONS MEDICAL ETHICS SOME GENERAL RULES

"Winter Session 1861-62 Nov 7th 1861 Professor Syme commenced his introductory address by referring to the importance of students attending to dissection, as without it, no man could hope to become a good surgeon It was only by dissecting that one could obtain a knowledge of the different organs, vascular and otherwise, of their positions and relations to each other, and it was mainly by means of it that he acquired the use of his hands in such manipulation If you cannot get human bodies to dissect, then by all means dissect the bodies of the lower animals, dogs, cats, rabbits etc He said it was quite a mistake to imagine that in order to become a good surgeon, men must be more than usually dexterous in the use of their hands No doubt manual dexterity was of some importance Yet he did not for a moment hesitate to say that more mechanical skill was necessary in the making of a chair than in almost any surgical operation "

"Another subject he especially urged upon students was the importance of adopting sound principles In order to become good practitioners we must adopt sound principles of theory and practice How many men went out into the world without any principles at all hence their want of success Let us adopt sound principles and our practice would become correspondingly sound "

Later, on 13th Jan 1862, he referred again to anatomy and emphasised its importance with another of his exciting stories "'In order to be good surgeons you must be good anatomists' Here the Pr told a good story of a surgeon who had been in practice for some time and yet never studied anatomy or had ever dissected a body, being called on to perform an operation for the relief of strangulated hernia The operation, which lasted nearly a day, had to be performed in a house, through the windows of which a crowd of children were staring and screaming (I failed to hear whether he had been able to give his patient the relief required without killing him) The ordeal which he had undergone, however, sent him to Edinburgh to learn anatomy This case, Pr Syme said, should make us all study anatomy diligently so as to give us confidence and ease of mind in our operations "

The next note raises delicate points of medical ethics and behaviour "He then told us of another case in which a medical man brought from a Provincial town a patient labouring under what he believed to be Hernia The other medical men in the same town also believed

that it was a hernia, whilst a Quack in the same town said it was a Hydrocele. Pr Syme on examining the man said that it was a Hydrocele, and on puncturing the Scrotum with a trocar showed the truth of his opinion. The medical man begged Pr S to say it was a hernia as the credit of the profession was at stake, the Quack being likely to rise in the estimation of the community. Pr S could not say what he believed to be untrue, but to the great joy of this medical man, the withdrawal of the water from the scrotum removed the support from the bowel above, which accordingly came down, saving the medical men's credit but proving fatal to the poor patient."

Some General Rules—In a case of severe disease of the foot in a girl, aet 14 years, Syme advised amputation of the foot. "The girl as soon as she heard this, cried out—'I'll no let you take it aff,' and made for the door, which the Pr did not attempt to contradict and reason her out of simply remarking after she and her mother went out—'Gentlemen, you will find it very useful in practice never to appear to go against the mind of your patient'."

In another case "he cautioned the class to avoid the pernicious habit of operating on all and every occasion. He said we ought never to operate unless we felt sure that benefit was likely to result from it."

In a case of psoas abscess he pointed out the dangers of opening this, and continued, "Now Gentlemen it is the duty of the Professional man to prolong life by all possible means, and if abstaining from doing anything comes within the category of 'possible means,' then *do nothing*. What I would recommend in this case is just to *do nothing*."

JAMES SYME, JOSEPH LISTER, THOMAS ANNANDALE

A last extract shows three successive Professors of Clinical Surgery at Edinburgh operating together on the second case of gluteal aneurism. "Friday, 14th June 1861. Pr Syme assisted by Pr Lister of Glasgow and Dr Annandale performed the operation today. On making incision in the aneurismal sac, the Blood spouted out to a great height. One jet lighted on the face of the student who administered the chloroform. Pr Syme immediately introduced his finger into the opening but did not succeed in finding the artery. He then enlarged the opening so as to admit his hand, but so firmly had the clotted blood of the old sac grown over it that he could not reach the artery so as to exercise the necessary pressure on it. He then opened freely into the sac and at once got the vessel under command. Dr A was particularly active. Loss of blood was great. Pr Syme thinks all will go well. 'Amen!'"

The student's prayer was answered, and the patient "a man, aet 44, from the neighbourhood of Carlisle" made a good recovery.

The extracts given above show something of the character and quality of this student notebook. The book itself, with its 115 closely

written pages in a free legible hand, is much more than an account of surgical principles and methods many of which are now obsolete—a dissected specimen dry and dead of out-of-date surgery. Its pages provide in dramatic form the whole human setting of a great surgeon at work. They give a day to day description of James Syme at the summit of his achievement and influence. The reader can see the working of the surgeon's mind in examination, and of his hands and the instruments of his hands in operation, and hears his words, few, clear, and incisive as his knife. Beside him are his assistants—the house surgeon and dressers—around, on the crowded benches, his students attentive and admiring, over the head of the surgeon bending to his work the invisible but felt aura of his experience and reputation. And in the centre are the patients, not mere cases tagged with their age and sex and disease but living creatures. The girl, aet 8 with a large tumour on the right jaw is introduced as “a little girl from Wales, in the very highest spirits, and carrying a large doll very gaily dressed” while case 44, a woman aet 35, with a boil on the thigh, under chloroform “began to sing a hymn in praise of her Maker, which seemed to tickle the fellows very much.”

Here in this notebook is life in a surgical theatre in Edinburgh in 1861—on the stage the surgeon, the assistants and the patients, in the amphitheatre the audience of students, their eyes and ears directed to the stage. In this surgical drama Syme dominates both stage and audience, and conducts the play. This student's notebook in its dramatic form is a valuable contemporary document of a bygone age in surgery and it draws from life a convincing portrait of James Syme as a great surgeon and a great teacher.

MEGALOBlastic ANÆMIA OF PREGNANCY AND THE PUERPERIUM

By JAMES R. CLARK, M.B., Ch.B., M.R.C.P. Ed

Part-Time Lecturer in Medicine, University of Edinburgh Senior Registrar
in Medicine, Royal Infirmary, Edinburgh

WALTER CHANNING¹ of Boston, Massachusetts was the first to recognise the disease now generally called megaloblastic anæmia of pregnancy and the puerperium. In a paper published in 1842 he distinguished it from anæmia due to loss of blood and noted its severe and often fatal character. Sir William Osler² in 1919 in his "Observations on the Severe Anæmias of Pregnancy and the Post-Partum State" drew attention to the fact that the disease differed from Addisonian pernicious anæmia in that when recovery took place it was permanent, although recurrence in a subsequent pregnancy was possible. The first description of the bone marrow in the disease was given in 1936 by Heilbrun³ who found it closely resembled that seen in untreated Addisonian pernicious anæmia. Meanwhile it was being realised that the blood picture did not always correspond exactly to that seen in Addisonian anæmia. Of Stevenson's⁴ 30 cases published in 1938, 12 had a colour index of unity or below unity. Moreover, Stevenson found achlorhydria in only 3 cases out of 19 examined. None of this series of cases had a bone marrow examination carried out, however. Davidson, Davis and Innes⁵ in 1942 emphasised the ways in which the disease could differ from Addisonian pernicious anæmia, and observed that it might respond poorly or not at all to treatment with refined liver extract. Fullerton⁶ in 1943 found a similar refractoriness to treatment with refined liver. Callender⁷ in 1944 reviewed the condition very fully, showed that the mean corpuscular volume might be within normal limits, and stressed the importance of marrow examination which might be the only means of establishing the diagnosis.

The Hæmatological Department of the Royal Infirmary of Edinburgh under the charge of Professor Davidson has treated since 1939, 43 cases of megaloblastic anæmia of pregnancy or the puerperium. Sixteen of these cases were published in 1942⁵ and 3 more in 1948⁸. Reference will now be made to 18 cases seen during the past seven and a half years (January 1944-June 1951) and the main clinical and hæmatological features of the disease will be described.

INCIDENCE

Fifteen of the 18 cases were referred from the Simpson Memorial Maternity Pavilion. These were distributed over the seven and a half years as shown in Table I.

A Honeyman Gillespie Lecture delivered on 22nd November 1951

The second column of figures represents the total yearly admissions to the Simpson. Since only hospital admissions are considered, no conclusions can be reached regarding the general incidence of the disease, but the figures will at least serve to show that it is not frequently

TABLE I

The Yearly Admissions to the Simpson Memorial Maternity Pavilion and the Number of Cases of Megaloblastic Anæmia Diagnosed there during the Same Period

Year	Number of Cases of Megaloblastic Anæmia	Total Admissions to S M P
1944	3	3875
1945	2	3873
1946	2	4519
1947	0	4255
1948	1	4321
1949	2	4357
1950	2	4371
1951	3	2184
To 30th June		

encountered. Nevertheless the 16 cases published by Davidson, Davis and Innes⁵ in 1942 were seen in two years during which period there were approximately 8000 confinements in the maternity hospitals concerned.

As to the experience of others, Evans⁹ in 1929 found no case in 4000 pregnancies. Boycott¹⁰ in 1936 found no case among 222 pregnant women, and in 1937 Reid and Mackintosh¹¹ found none in 1108 pregnancies. Thompson and Ungley¹² this year (1951) reviewed 45 cases which had been seen during the past seventeen years. No data about incidence are, however, available.

With regard to the relative frequency of the disease as compared with Addisonian pernicious anæmia, the commonest form of megaloblastic anæmia in this country, during the seven and a half years under review, 322 cases of the latter disease were seen at the Blood Clinic and associated wards, approximately 18 cases for every case of megaloblastic anæmia of pregnancy.

CLINICAL FEATURES

Age—The age varied between 21 years and 41 years, the mean age being 33 years. These figures contrast, as is the rule^{4, 12}, with those seen in Addisonian pernicious anæmia which has its greatest incidence between the ages of 40 and 70¹⁷.

Previous Pregnancies—Five of the women were primigravidæ, while 12 had borne two or more children, the condition, as usual, being more commonly seen in those who have had previous pregnancies^{4, 7, 12}.

Diarrhœa of prolonged duration was found in 2 cases (Nos 16, 17), no specific organism being isolated in the stool of either

Edema of varying degree is of quite common occurrence^{4, 7} In 4 cases œdema was marked but 3 of these suffered from pre-eclamptic toxæmia

A Sore Tongue was complained of in 7 cases, of these, 5 were abnormal on inspection, showing either acute glossitis or atrophy of the papillæ In addition the tongue was atrophic in 6 other cases, without being sore Thus the tongue was sore and/or atrophic in 13 cases out of 18

Koilonychia was seen in no case

Enlargement of Spleen—Only 1 patient (No 13) had a palpably enlarged spleen

Enlargement of Liver was seen in 2 cases (Nos 5 and 16)

Nervous System—Examination of the nervous system revealed no abnormality except in 1 case (No 10) who exhibited a mild hemiparesis which had followed diphtheria at the age of 6 The rarity of sub-acute combined degeneration in megaloblastic anæmia of pregnancy¹² as compared to its not unusual occurrence in Addisonian pernicious anæmia, has long been recognised

Serum Bilirubin or icteric index examinations were carried out in only 3 patients, the highest figure for the latter being 11 units Some of the patients showed an apparent degree of icterus similar to that often seen in pernicious anæmia In general such an appearance is more common in the latter disease⁷

A Test Meal was carried out in all but 2 of the cases Free hydrochloric acid was found in 10 cases and a histamine-fast achlorhydria in 6 This is one of the most significant ways in which the disease differs from Addisonian pernicious anæmia where achylia is always found¹³ The 6 cases with achlorhydria had atrophic tongues Of the 10 cases with free acid, only 3 had atrophic tongues

Diet During Pregnancy—A full analysis of the diet was requested from the Dietetic Department in 2 cases only (Nos 14, 15) In both the diet was found to be inadequate For example in Case 15 "the total number of calories was inadequate, the protein below the recommended allowance, calcium below normal and vitamin A only half the recommended amount Thiamine was quite inadequate and the B complex low" In addition an inadequate diet was taken by 5 patients on account of continued vomiting In another case the diet was judged to be grossly lacking in calories, first-class protein and vitamins Two patients ate little food on account of poor appetite and nausea No fault was found with the diet in 4 cases and no information is available in 3 Thus the diet during pregnancy was unsatisfactory in at least 8 cases Although this state of affairs is common¹² its ætiological significance is not established This matter will be referred to again

HÆMATOLOGICAL FINDINGS

The state of the blood in each case at the time of diagnosis is shown in Table IV

TABLE IV

Main Hematological Findings

Case	Hb %	Hb gm%	RBC (mil /cmm)	CI	WBC cmm	PCV %	MCV μ	MCHC %
1	70	10.36	3.08	1.14	8,200			
2	28	4.14	1.18	1.19		13.5	114.4	30.6
3	40	5.92	1.97	1.02	8,600	17.5	88.8	33.2
4	42	6.21	2.91	0.72	5,800	19	65.3	32.6
5	38	5.62	1.45	1.30				
6	52	7.69	2.76	0.94	8,200	29	105.1	26.5
7	60	8.88	2.33	1.29	7,200	24	103.0	37.0
8	48	7.10	1.76	1.36	8,800	21	119.2	33.8
9	30	4.44	1.65	0.90	10,200	17	103.0	26.1
10	50	7.40	2.94	0.84	4,000	22	74.8	33.6
11	44	6.51	2.03	1.08	8,200	18	88.6	36.1
12	52	7.69	2.19	1.19	6,000			
13	21	3.10	1.18	0.87	6,000	10	84.7	31.0
14	35	5.18	2.13	0.82	5,600	16.5	77.4	31.4
15	50	7.40	2.78	0.91		22	79.1	33.6
16	37	5.47	1.95	0.94	4,400	13	66.6	42.0
17	58	8.58	3.50	0.82	6,200	21	60.0	40.8
18	34	5.03	2.05	0.83	5,000	16.1	78.5	31.2

PCV = packed cell volume

MCV = mean corpuscular volume

MCHC = mean corpuscular hæmoglobin concentration

It will be noted that in 2 cases (Nos. 16 and 17) the MCHC was apparently higher than the theoretical maximum

Hæmoglobin—The lowest Hb. was 21 per cent (3.1 gm per cent) and the highest 70 per cent (10.36 gm per cent). The mean was 44 per cent (6.5 gm per cent). (In every case standardisation was the same, 100 per cent = 14.8 gm per cent.)

Red Cell Count—The lowest initial figure seen was 1.18 mil /c mm and the highest 3.5 mil /c mm. In 6 cases the red count was over $2\frac{1}{2}$ mil /c mm. The mean figure was 2.21 mil /c mm.

Colour Index—This ranged between 0.72 and 1.36 with a mean of unity (1.008). The normal range may be regarded as 0.85-1.15¹⁴. On this basis 5 cases had a colour index above normal, 8 had a colour index within the normal range and 5 were below it.

Mean Corpuscular Volume—This was estimated in 15 cases. The results varied between 119.2 μ and 60.0 μ with a mean of 87.2 μ . The normal range may be taken as 78-94 μ ¹⁵ so that on this basis 5 gave figures above normal, 5 below normal and 5 within the normal range. Judging from the stained film alone macrocytosis was present in 6 cases. The colour index was raised in 5 of these cases and the mean corpuscular volume in 4 but no mean corpuscular volume reading was available in the other two. The MCV was raised in only

one case in which macrocytosis was not suggested by either the film or the colour index

By all methods employed, therefore, macrocytosis was detected in only 7 cases out of the 18

The absence of macrocytosis in a significant proportion of cases has been generally recognised,^{4, 5, 7, 12} and has an obvious bearing on the problem of diagnosis

Hypochromia—The colour index is of limited value in megaloblastic anæmia of pregnancy in determining incomplete saturation of the erythrocytes with hæmoglobin. A better method is to calculate the mean corpuscular hæmoglobin concentration. The normal range for this is 32-38 per cent^{15, 16}. Six cases gave figures below this range but only 2 were below 30 per cent. A degree of iron deficiency is frequently found in the untreated case¹² while in untreated Addisonian pernicious anæmia this is rare. Detection of iron deficiency by examination of the stained film may present considerable difficulty. Evidence

FIG 1 —Peripheral blood —dimorphic anæmia from a case of megaloblastic anæmia of pregnancy

FIG 2 —Bone marrow —showing early megaloblasts and one late megaloblast (Case 14 before treatment)

FIG 3 —Bone marrow —showing an intermediate megaloblast (Case 13 after refined liver therapy and before treatment with folic acid)

FIG 4 —Bone marrow —showing change to the hyperplastic normoblastic state (Case 13 following folic acid therapy)

FIG 5 —Bone marrow —showing late normoblasts following folic acid therapy (Case 14) × 950

of iron deficiency appeared to be seen in 6 cases, but could be correlated with the M C H C in only 3 of these. Nevertheless in some cases with a dimorphic peripheral blood picture, inspection of the stained film may be of more value in diagnosis than estimation of the M C H C or colour index (Fig 1)

White Blood Count—A wide range of normality is recognised, 4000-11,000¹⁷. W B C counts before treatment are available in 15 cases, and in no case did the figures fall beyond these limits. The low white counts frequently seen in pernicious anæmia were not found.

No platelet counts were carried out in any of the cases. None of this series showed purpura or other hæmorrhagic features.

Examination of the Stained Blood Film—This procedure often failed to suggest the true nature of the anæmia. As already stated, macrocytosis was well marked in only 6 cases. Nevertheless the detection of an occasional macrocyte in other cases with a normal M C V was the clue to further investigation. Inspection of the film was also of value in those cases with a dimorphic anæmia as already stated.

Immature white cells and nucleated red cells were occasionally seen in the present series. Case 8 showed a few metamyelocytes and



FIG 2



FIG 3

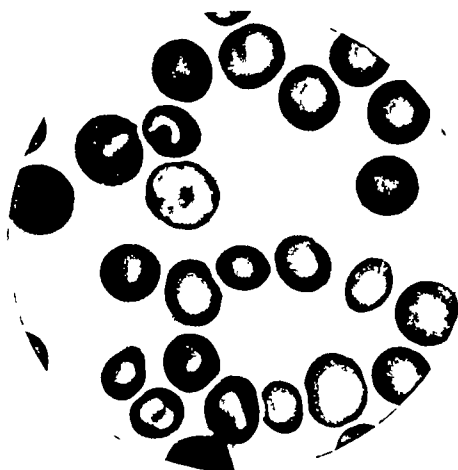


FIG 1

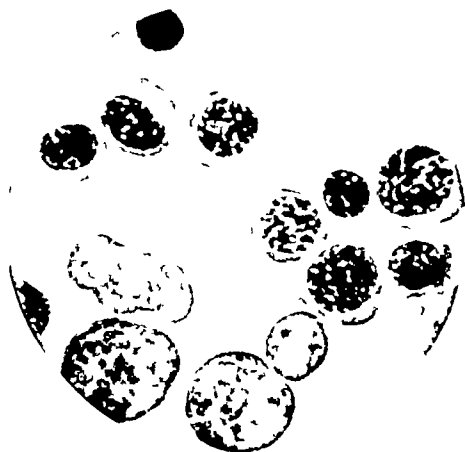


FIG 4



FIG 5

normoblasts, while quite numerous myelocytes and normoblasts were seen in the peripheral blood of Case 15 during the course of a superadded bronchopneumonia

Bone Marrow—Every case had at least one bone marrow examination carried out and all were megaloblastic before the commencement of treatment (Figs 2 and 3) The terminology employed is that of Israels^{18, 19}

Repeat bone marrow examinations (Fig 4) were carried out in a number of cases in order to assess as early as possible response to treatment especially when the time available before the confinement was limited It has been clearly shown that the marrow exhibits the first detectable sign of response which is a change in the appearance of the megaloblastic nuclei, and precedes by a significant period of time changes in the reticulocyte and red cell level²⁰

After a response had occurred as shown by reticulocytosis and more importantly by a rise in the red cell count, not every case was submitted to a further marrow examination, it being a reasonable inference that the marrow had reverted to the normal state However, a second sternal puncture was done in 6 cases (Nos 12, 13, 14, 16, 17, 18) and the bone marrow had reverted to the normoblastic state in all of these (Fig 5)

DIAGNOSIS

No case was accepted for this series unless the bone marrow was megaloblastic

Since it is clear that a macrocytic peripheral blood picture is by no means the rule, and in fact was present in only about one-third of the present series, it is obvious that many cases will be missed if this feature alone is relied upon for diagnosis Some cases have a frankly hypochromic blood picture The M C V may even be lower than the normal range It is for this reason that diagnostic difficulties occur, because simple iron deficiency anæmia is a relatively common blood disorder during and after pregnancy and it is obviously impracticable to examine the marrow of every anæmic pregnant woman Further, some of these simple iron deficiency anæmias may be remarkably resistant to oral treatment with iron²¹ so the fact that iron therapy has failed is not certain evidence that some other ætiological factor is present It is advisable, however, to examine whenever possible the bone marrow of all pregnant women with an apparently refractory iron deficiency anæmia who have a red cell count of under $3\frac{1}{2}$ mil One of the present series had a red count of $3\frac{1}{2}$ mil, which is above the lower limit of the physiological anæmia of pregnancy according to some workers²²

When the anæmia has been proved to be megaloblastic the diagnosis is still not established In all probability a pregnant or puerperal woman who has such a marrow suffers from the disease in question but some other possibilities exist Women with Addisonian pernicious anæmia may become pregnant, though this is rare^{8, 23 24} The finding

of free hydrochloric acid in the gastric juice excludes this disease, but some cases of megaloblastic anæmia of pregnancy also show a histamine-fast achlorhydria. Their final distinction from Addisonian pernicious anæmia must then depend on their ability to remain well without treatment, as shown by serial blood examinations carried out at intervals for two years. Finally, other causes of megaloblastic anæmia must be borne in mind, for example a woman with the sprue syndrome (tropical sprue or idiopathic steatorrhœa) may become pregnant. The distinction may usually be made on clinical and biochemical grounds. Nutritional megaloblastic anæmia and its relationship to megaloblastic anæmia of pregnancy will be considered later.

TREATMENT

Various forms of treatment were employed in the present series. For convenience in assessment, cases are said to "respond" if a rise in the red cells and hæmoglobin follows treatment after a preliminary period of observation has revealed a stationary or falling blood level. The reversion of the bone marrow from the megaloblastic to the normoblastic state is an essential part of the response. As already stated this change was inferred in some cases from the degree of improvement in the peripheral blood. In other cases, including any where doubt existed, the marrow change was proved by sternal puncture. Cases which "respond" are subdivided into two groups, "satisfactory" where the red cell increase reaches or surpasses a certain chosen standard, and "unsatisfactory" where it fails to attain this standard. The formula of Della Vida and Dyke²⁵ has been chosen for purposes of comparison.

Refined Liver Extract—(Table V). Well known commercial extracts for parenteral administration were used and most of the batches employed had been tested for potency in cases of Addisonian anæmia. Eleven cases in all were treated in this way. Of the 5 treated with liver extract before delivery, none responded. Of the 6 cases where treatment was instituted in the puerperium or immediately before delivery (Case 1) 3 failed to respond. One response was "satisfactory," one "unsatisfactory" and one could not be assessed accurately owing to blood transfusion. Thus the results of treatment with purified liver extract are in this series extremely poor. This experience has been shared by others,^{4, 6, 7, 12, 26, 27, 28} and contrasts with the results obtained in Addisonian pernicious anæmia. In cases 2 and 4 it is possible that the quantity of liver extract used was insufficient to prove complete refractoriness to this treatment in the absence of bone marrow confirmation. This quantity, however, would have produced a "satisfactory" response in Addisonian pernicious anæmia. In case 5 which was treated during the puerperium, a satisfactory response might well have been obtained had a larger amount of liver extract been administered.

Vitamin B₁₂—(Table V) There was no reason to suppose when vitamin B₁₂ was isolated in 1948^{29 30} that it would be any more effective in the treatment of megaloblastic anæmia of pregnancy and the puerperium than refined liver extract. Nor has this proved to be the case^{12 31 32 33}. Five of the present series were treated with B₁₂ in doses varying from 10 µg to 120 µg. Two cases were treated before and 3 after delivery. There was no response in any of these cases.

TABLE V

Results of Treatment with Refined Liver Extract and Vitamin B₁₂. Cases are Divided into Two Groups according to whether Treatment was given before Delivery or After (Case 1 is included in the latter Group)

Case	Treatment Started		Treatment	Dosage	Duration	Average weekly rise in RBC during first 2 weeks of treatment mil /c mm	Expected Rise in RBC (Della Vida)	Response
	Before Delivery	After Delivery						
2	12 weeks		Refined liver ext	4 ml weekly	1 week	no rise		absent
4	14 days		ditto	4 ml weekly	1 week	no rise		absent
6	8 weeks		ditto	6 ml weekly	9 days	fall *		absent
9	3 weeks		ditto	4 ml weekly	3 weeks	no rise *		absent
13	years		ditto	1½ ml weekly	until 23rd wk of preg	fall *		absent
12	4½ weeks		B ₁₂	10 µg in all	2 weeks	no rise		absent
15	6 days		B ₁₂	40 µg in all	16 days	no rise *		absent
1	3 days		Refined liver ext	4 ml weekly	3 weeks	no rise		absent
5		14 weeks	ditto	1 ml in all	2 weeks	0.45	0.588	unsatisfactory
7		12 days	ditto	4 ml in all	2 weeks	no rise *		absent
8		8 weeks	ditto	4 ml weekly	3 weeks	cannot be assessed		present
10		2 weeks	ditto	6 ml weekly	1 week	fall *		absent
11		3 weeks	ditto	6 ml weekly	continuing	0.465	0.466	satisfactory
14		5 days	B ₁₂	20 µg in all	2 weeks	no rise *		absent
16		3 days	B ₁₂	120 µg in all	1 week	fall *		absent
18		2 weeks	B ₁₂	80 µg in all	2 weeks	fall *		absent

* Sternal puncture performed at end of trial period (megaloblastic in each case)

Proteolysed Liver (Table VI) was given in 4 cases, 3 of which had failed to respond to refined liver. Proteolysed liver was introduced in 1943 by Davis, Davidson, Riding and Shaw,³⁴ and is a papain digest of whole liver suitable for oral administration. Two cases were treated before delivery and both responded although, in 1 the red cell increment was subnormal and the response, therefore, labelled "unsatisfactory". Two cases treated after delivery responded "satisfactorily". As will be seen these results are in every way comparable to those obtained with folic acid.

Pteroylglutamic Acid—(Folic acid) (Table VI) was the method of treatment in 8 cases, 4 of which had failed to respond to B₁₂. Doses varied between 10 mg and 45 mg daily. A response occurred in every

case Of 3 treated before delivery the response in 2 could not be assessed accurately on account of blood transfusion The third case (No 13) showed a "satisfactory" response

TABLE VI

Results of Treatment with Proteolysed Liver (P L) and Pteroylglutamic Acid (P G A) Cases are Divided into Two Groups as explained above, Table V

Case	Treatment Started		Treatment	Dosage	Average weekly rise in RBC during first 2 weeks of treatment mil /c mm	Expected weekly rise in RBC in RBC (Della Vida) mil /c mm	Response
	Before Delivery	After Delivery					
2	11 weeks		P L	40 gm daily	0 745	0 724	satisfactory
6	7 weeks		P L	40 gm daily	0 215	0 417	unsatisfactory
12	3 weeks		P G A	10 mgm daily	Blood transfusion prevents assessment		
13	17 weeks		P G A	30 mgm daily	0 675	0 552	satisfactory
17	4 weeks		P G A	30 mgm I M I	Blood transfusion prevents assessment		
3		1 week	P L	20 gm daily	0 60	0 509	satisfactory
4	5 days		P L	20 gm daily	Blood transfusion prevents assessment		
9		2 weeks	P G A	20 mgm daily	0 895	0 595	satisfactory
10		3 weeks	P G A	30 mgm I M I	0 690	0 466	satisfactory
14		3 weeks	P G A	20 mgm daily	0 110	0 442	unsatisfactory
15		10 days	P G A	45 mgm daily	0 595	0 517	satisfactory
16		8 days	P G A	20 mgm daily	0 185	0 564	unsatisfactory

Of 5 cases treated after delivery the response was "satisfactory" in 3 and "unsatisfactory" in 2 (Cases 14 and 16) One of these (Case 16) was seriously ill with an intercurrent infection while treatment was being given, and has already been referred to

Good results have in general been reported with folic acid 8, 31, 32, 33, 35, 36

TABLE VII

Summary of Results of Treatment with Refined Liver Extract, Vitamin B₁₂, Proteolysed Liver, Pteroylglutamic Acid (P G A) and Citrovorum Factor

Treatment	Number of Cases Treated	Response	Failure
Refined liver extract	11	3	8
B ₁₂	5	0	5
Proteolysed liver	4	4	0
P G A	8	8	0
Citrovorum factor	1	1	0

Case 18 was treated with *Leuconostoc citrovorum* factor³⁷ A "satisfactory" response was obtained Details of this and another case of megaloblastic anæmia of pregnancy, treated by the same

substance, will be published shortly by Davidson and Girdwood * Citrovorum factor which is probably identical with folic acid,^{38, 39} is known to be active in Addisonian anæmia,^{40 41} but no report has yet appeared about its effectiveness in megaloblastic anæmia of pregnancy

A summary of the results of treatment is given in Table VII

Some of the cases, especially those showing an associated iron deficiency before the commencement of treatment, failed to continue to improve after an initial response until iron was also administered

PROGNOSIS

Before the introduction of proteolysed liver and folic acid, deaths frequently occurred. Repeated blood transfusion was the main life-saving procedure

The outlook for the mother is now good provided the diagnosis is not so long delayed that labour ensues at a dangerously low blood level. Every one of the present series made a complete recovery, although 2 (notably Case 16 already mentioned) were seriously ill for a time with intercurrent infections

Three women gave birth to still-born infants, but one of these was an anencephalic fetus. Of those babies born alive, including two sets of twins, all are now well except for one infant which died at the age of seven weeks of an unknown cause

FOLLOW-UP

A follow-up examination (Table VIII) of this series of cases was carried out. In 2 cases (Nos 3 and 8) it was not found possible to get in touch with the individual concerned. A further case (No 18) had been too recently treated to include in the follow-up investigation

Further Pregnancies had occurred in 3 patients (Cases 4, 7 and 10). Case 7 had 2 further pregnancies and although she was not seen by us during the first of these, the following information was obtained. When apparently not more than two months pregnant she became anæmic. No bone marrow investigation was carried out, but the Hb was 70 per cent and the R B C 2.64 M. The film was macrocytic. Folic acid was administered and the Hb rose to 92 per cent and the R B C to 4.7 M. About this time she had an abortion. From then until the time of her next pregnancy no treatment was given. A healthy full-time child was born precisely one year later. She was seen during the course of this pregnancy at the Blood Clinic and found to have a mild degree of iron deficiency anæmia, the R B C never falling below 4.3 M. No folic acid was given.

Case 10 was treated in another hospital. When six months pregnant the Hb was 66 per cent and the R B C 2.9 M. The blood film suggested macrocytosis. No marrow examination was done but folic

* *Lancet* in Press

acid was administered with good clinical improvement. The patient subsequently gave birth to a healthy full-time child.

Thus there is reason to believe that 2 of the only 3 patients of the series known to have had subsequent pregnancies developed megaloblastic anaemia again. Since one case had gone for two years and the other for two and a half years without treatment this development must be regarded as a true recurrence rather than a relapse in each case.

Of the 12 patients who had not conceived again 6 had purposely avoided pregnancy.

Hematological State

Erythrocyte Level—Every case had a red cell count of 4.3 M or higher, with the single exception of Case 12. Here the count was 3.78 M and a bone marrow examination was therefore carried out, this proved to be normoblastic. Thus no patient showed any sign of a relapse to megaloblastic blood formation.

Time without Treatment—Five patients had been without treatment for six years or longer, and a further 5 for one year or longer, the actual times being shown in Table VIII. Four patients had gone for

TABLE VIII

Details of Follow-up Investigation of 16 Cases of Megaloblastic Anaemia of Pregnancy or the Puerperium

Case	Time since Parturition	Further Pregnancy	Further Megalo-blastic Anaemia of Pregnancy	Time since cessation of Treatment	Hb % & gm %	RBC mil /cmm	CI	MCV cu	MCHC %	CNS
1	7½ years	0	0	7½ years	90 13 22	4 71	0 95	76 6	37 0	No abnormality
2	6½ years	0	0	6½ years	93 13 76	5 46	0 85	75 0	33 5	ditto
4	6 years	2	0	6 years	76 11 24	4 46	0 85			ditto
5	6½ years	0	0	6 years	98 14 5	4 78	1 03	78 4	38 6	ditto
6	6 years	0	0	6 years	96 14 2	4 78	1 0	83 6	35 5	ditto
7	5½ years	2	+	3 years	70 10 36	4 54	0 77	76 0	30 0	ditto
9	3½ years	0	0	3 years	83 12 28	4 33	0 96	83 1	34 1	ditto
10	3½ years	1	+	8 months	81 11 98	4 53	0 9			I S Q
11	2½ years	0	0	Treatment continues	90 13 32	5 00	0 9	77 0	34 6	No abnormality
12	2 years	0	0	2 years	73 10 8	3 78	0 96	71 4	40 0	ditto
13	1 year	0	0	1 year	96 14 2	4 65	1 03	94 6	32 2	ditto
14	1½ years	0	0	1½ years	79 11 69	5 04	0 78	79 3	29 2	ditto
15	1 year	0	0	7 months	95 14 06	4 83	0 98	84 8	34 2	ditto
16	7 months	0	0	5 months	98 14 5	5 95	0 82	67 2	36 2	ditto
17	3 months	0	0	3 months	87 12 87	4 46	0 97	96 4	29 9	ditto

less than one year without treatment, since all 4 had had their megaloblastic anaemia less than one year before. One patient (Case 11) had not stopped treatment owing to a misunderstanding.

Distinction from Addisonian Pernicious Anaemia—All 10 cases with free hydrochloric acid can be excluded. Of the other 8, 4 have maintained a normal erythrocyte level without any treatment for two years or longer and may also be excluded. Of the remaining 4, Case 10

had previously kept well for two years without treatment between her first and second attacks of megaloblastic anæmia of pregnancy and she has now been eight months without treatment following the latter Case 15 has kept well for seven months without treatment

Taking the whole series of 18 cases, therefore, Addisonian pernicious anæmia has not been finally excluded in 3, Case 3 because nothing is known of her, Case 11 because treatment had not been stopped, and Case 15 because insufficient time has elapsed for a final decision to be reached

Nervous System—This was examined in 15 cases and no abnormality was detected except that the hemiparesis already noted in Case 10 was, of course, unchanged

General State—All 15 cases followed up were well, and general examination was negative except where otherwise stated

Iron Deficiency Anæmia—It will be observed that although the red cell level was satisfactory in all save Case 12 already mentioned, mild degrees of iron deficiency anæmia were common This is interesting in that many cases have a vague history of pallor, tiredness, etc., prior to pregnancy and that during pregnancy an associated iron deficiency is often found to accompany the megaloblastic anæmia Nevertheless, the 2 cases with the most marked hypochromic anæmia at follow-up (Cases 7 and 14) had little or no evidence of this during their pregnancy anæmia and neither of the 2 (Cases 6 and 9) with the most obvious associated iron deficiency during pregnancy, showed iron deficiency at follow-up There is thus no correlation in this respect amongst the present series of cases

DISCUSSION

At this point it may not be inappropriate to consider a much commoner disease similar to, or, as some ⁴² ⁴³ think, identical with the megaloblastic anæmia of pregnancy and the puerperium seen in temperate zones Amongst the many names that have been applied to it are tropical macrocytic anæmia,⁴⁴ nutritional macrocytic anæmia,⁴⁵ and more recently nutritional megaloblastic anæmia⁴² The disease, which has received careful study especially from Wills and her associates,⁴⁶⁻⁵³ is a megaloblastic anæmia affecting pregnant and non-pregnant females and also males A similar anæmia has been described in Macedonia⁴⁵ and in Africa⁵⁴ Cord changes are not seen, free hydrochloric acid is often present and the age group is younger than in Addisonian pernicious anæmia⁴⁸ Wills found that the condition responded well to marmite, an autolysed yeast product⁴⁴ She found that dried yeast, watery extracts of yeast and preparations of vitamin B complex from other sources were inactive⁵³ Response to liver at first seemed satisfactory⁴⁸ but later it was found that refined liver extracts were often ineffective⁵⁵ As is the case with megaloblastic anæmia of pregnancy and the puerperium in this country there has been a lack of uniformity in the response of the disease to different forms of treatment

Thus Fairley and his associates⁴⁵ working in Macedonia, found that much larger quantities of marmite or crude liver might be required in their cases than in those seen in India. Even then the blood level might improve only slowly. There was a difference, too, amongst cases seen in India, Mudalier and Rao⁵⁶ for instance, getting no response to treatment with marmite. Further, while Wills^{55, 57, 58} and Watson and Castle⁵⁹ found refined liver extract ineffective, Moore and his colleagues⁶⁰ in the United States and Patel and Bhende⁶¹ in India had a high measure of success using refined liver extract. Vitamin B₁₂ has also been found to be active in this same disease^{62, 63, 64}. The response to pteroylglutamic acid, however, seems to be uniformly satisfactory⁶⁵⁻⁶⁹.

Watson and Castle⁵⁹ considered that the diversity of results following treatment suggested that more than one type of nutritional macrocytic anæmia might occur and that deficiency of a substance found in autolysed yeast which they suggested be called "Wills' factor" might be the cause of one. Another type might be due to extrinsic factor deficiency. The work of Day *et al*,⁷⁰ Wilson *et al*⁷¹ and Furman *et al*⁷² suggested that Wills' factor might be folic acid, but this view does not find general acceptance,^{73, 74} Ungley⁷⁵ for instance, observing a response in a case of megaloblastic anæmia of pregnancy treated with an alcoholic extract of yeast containing less than 40 µg of folic acid per dose.

Kothari and Bhende⁴³ feel that the evidence is overwhelmingly in favour of tropical macrocytic anæmia being essentially nutritional in origin and Bhende⁴² accordingly suggests that the name nutritional megaloblastic anæmia be used. Kothari and Bhende consider that there is no difference between this disease and the megaloblastic anæmia of pregnancy seen in temperate climates. Pregnancy they suggest may precipitate a nutritional deficiency by increasing the requirements of a dietary factor present in "borderline" amounts. Remission following pregnancy could also be explained along these lines.

Certain objections may be made to regarding the two diseases as identical. That seen in this country is never found to affect patients other than pregnant and recently pregnant women. Pregnant women may develop it who have been taking a diet which appears to be beyond criticism, while others who have been taking a very bad diet may never succumb to the disease. Evidence of faulty intestinal absorption as a possible factor in producing a conditioned nutritional deficiency has not been convincing. Two of the present series of cases (Nos 9 and 17) with diarrhoea had a fat balance test⁷⁶ carried out which revealed no impairment of absorption, but it must be admitted that this method of examination may be unreliable. The older theories as to causation of the disease—a hæmolytic agent,² a temporary deficiency of extrinsic factor⁵³ or intrinsic factor⁷⁷—have had to be discarded, at least with regard to the ætiology of the majority of cases.

Does the response of megaloblastic anæmia of pregnancy to various

forms of therapy shed any light upon the ætiology? Many kinds of treatment have been used, including whole liver,^{6, 78} refined liver extract,^{4, 5, 78} crude liver,⁷⁸ proteolysed liver,⁸⁰ hog's stomach,^{4, 79} yeast,⁷⁵ marmite,⁷⁸ B₁₂,^{31, 32, 33} folic acid^{8, 31, 32, 33, 35, 36}

Amongst the most successful of these have been whole liver, proteolysed liver and folic acid. The possibility naturally arises of folic acid being the factor common to these three. Folic acid is present in whole liver and proteolysed liver, but virtually absent from refined liver extract. Sufficient folic acid may be present in whole liver to account for its success, but in proteolysed liver the quantity present is of more doubtful significance.⁸⁰ However, this possibility cannot be excluded. Vilter and his associates⁷³ suggest that the active substance in proteolysed liver and some crude liver extracts is Wills' factor and that this is, as already stated, not folic acid. These workers think that Wills' factor may function with folic acid in the synthesis of nucleic acid by activating the formation of purines and pyrimidines, for example thymine, by methylation of uracil. If this were the case, vitamin B₁₂ would not be expected to be effective in a case of megaloblastic anæmia of pregnancy with a Wills' factor deficiency as it is believed to activate the formation of nucleosides such as thymidine from the purines and pyrimidines already formed and so play an important part in a later stage of the synthesis of nucleic acid.

Since, as far as can be known, folic acid is effective in all cases of megaloblastic anæmia of pregnancy and the puerperium in causing the bone marrow to revert to the normoblastic state and bringing about a rise in the blood level, and since folic acid in the form of its conjugates is a constituent of the normal diet, it is tempting to conclude that the disease is due to a deficiency of this substance. Further, folic acid has been shown experimentally to be necessary during reproductive processes⁸¹ and there is evidence of an increased requirement for this substance during pregnancy.^{82, 83}

It is possible, however, that more than one type of deficiency occurs, in other words, as suggested by Thompson and Ungley,¹² that cases of megaloblastic anæmia of pregnancy and the puerperium do not form one homogeneous group.

CONCLUSIONS

Although much remains to be discovered about the ætiology of megaloblastic anæmia of pregnancy, enough is known of the disease to permit certain conclusions of practical importance to be drawn.

The disease is uncommon but probably less so than generally supposed.

The importance to the mother and unborn child of early diagnosis and proper treatment cannot be over stressed.

Many cases will be missed if a macrocytic anæmia is made the main criterion of diagnosis and no marrow examination is carried out.

Folic acid is the treatment of choice, and is simple and effective. It should be supplemented with iron.

Treatment may be discontinued after the birth of the child when a normal blood level has been reached.

Cases with a histamine-fast achlorhydria should be seen at intervals for two years after the cessation of treatment to exclude the possibility of their having Addisonian pernicious anæmia.

The occurrence of megaloblastic anæmia during one pregnancy does not contraindicate another pregnancy provided adequate ante-natal care is available and the blood is examined at regular intervals.

I wish to thank Professor Kellar, Dr Fahmy and Dr Douglas Miller for permission to refer to their cases and for access to obstetrical records. I am grateful to Professor Davidson for advice and encouragement and to Miss S T Lindsay for the many blood counts involved.

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OBITUARY

EDWIN BRAMWELL, M D , C M , F R C P Lond & Edin ,
LL D Edin , Hon M D Melb , F R S E

PROFESSOR BRAMWELL died in Edinburgh on 21st March after a long and painful illness

He was the eldest son of Sir Byrom Bramwell, M D , F R C P E , LL D , and was born in North Shields in 1873 His early education was at Cheltenham, and from there he entered the University of Edinburgh to study Medicine After qualifying in 1896 he became resident physician to Professor Grainger Stewart in the Royal Infirmary and at the same time was elected one of the Presidents of the Royal Medical Society A period of continental travel was common in these days, and Bramwell followed the fashion by studying for a time at Frankfurt, Freiberg, Heidelberg and Paris On returning to Britain in 1899 he acted as Resident Medical Officer at Queen Square Hospital for Nervous Diseases The following year he took the Membership of both the Edinburgh and the London Colleges of Physicians After his return to Edinburgh his first appointment was as Assistant Physician to Leith Hospital in 1902, and in 1907 he was elected Assistant Physician to the Royal Infirmary

Post-graduate education in Medicine always interested him deeply He became secretary to the joint committee appointed by the University and the Royal Colleges to arrange and supervise post-graduate courses Later he acted as chairman of this committee His enthusiasm and his painstaking work on behalf of the committee made a success of the scheme, and to him more than to any other individual is due the reputation and high standard of the post-graduate courses in Edinburgh

Edwin Bramwell qualified as an extra-mural lecturer in medicine and for a number of years was associated with his father in running a highly successful course in systematic medicine

During the war of 1914-18 he was mobilised as a Captain in the second Scottish General Hospital at Craigleith (now the Western General) and the Royal Victoria Hospital Here he acted as physician and neurologist and was in charge of those who suffered from shell shock When the War Office set up a committee to inquire into shell shock and advise the Army on such cases Bramwell was invited to become a member

In 1919 he was promoted to full charge of Medical Wards in the Royal Infirmary He soon attracted a large clinic for nervous cases and became recognised as a reliable and helpful consultant The University appointed him lecturer in Clinical Neurology and he gave regular courses of lecture demonstrations which, though voluntary, attracted large numbers of under graduates His work in the wards was of a very high standard and he was an excellent teacher He was always courteous towards his patients, even the most stupid and trying, and never caused them embarrassment before the students His success with neurotic or hysterical cases was often dramatic, and his careful handling of patients must have impressed many generations of students From his assistants he demanded the highest standards of medical



EDWIN BRAMWELL

work and he instilled into them a full sense of the responsibilities of the profession and a feeling that nothing but the best was acceptable

When Professor Darby Boyd died prematurely in 1922, Edwin Bramwell was selected to succeed him in the Moncrieff Arnott Chair of Clinical Medicine. This appointment included the chairmanship of the Clinical Medicine Board, and his tact and charm carried the Board successfully through difficult times. He continued his interest in neurology, and his voluntary lecture-demonstrations attracted large numbers of students and post-graduates. After fifteen years in charge of wards he resigned his chair in 1934 and was appointed Consulting Physician.

Professor Bramwell was well known outside Edinburgh and he was recognised as one of the leading neurologists in Britain. Many honours came to him. He was invited to deliver the Morison Lectures of the Royal College of Physicians of Edinburgh (1916 and 1917), the Bradshaw Lecture (1925) and the Croonian Lecture (1937) of the College of Physicians of London. During a tour of Australia in 1935 he gave the Halford Oration at Canberra and was made an honorary M.D. of Melbourne. The University of Edinburgh gave him the degree of LL.D. in 1937. He was President of the Royal College of Physicians of Edinburgh during the years 1934 and 1935. An original member of the Association of Physicians he was invited to become a corresponding member of the Neurological Societies of Paris and Philadelphia and at various times he was president of the Association of British Neurologists, the Neurological Section of the Royal Society of Medicine and of the Section of Neurology of the B.M.A. (1927 and 1935).

Professor Bramwell was a first-class clinician, a close and patient observer and a prolific writer. His painstaking and extensive study of encephalitis lethargica gained him the degree of M.D. in 1919.

He was happy in his home life. His wife, the elder daughter of Professor J. D. Cunningham, was a loyal support, a charming hostess and a devoted nurse. To her and to his son and daughters we extend our deepest sympathy, and we mourn the passing of a charming personality and a much beloved colleague.

NEW BOOKS

Brain Metabolism and Cerebral Disorders By HAROLD E. HEMWICH, M.D.
Pp 452, with 52 illustrations London Bailliere, Tindall & Cox 1951
Price 46s 6d

This book might be described by a clinician as complementary to the study of neurology, in that it explains the ancillary sciences, the description being essentially, as indeed the title suggests, from the viewpoint of physiology and biochemistry. Perhaps, regretfully, these aspects have become increasingly important in modern conditions, yet it is with a sense of nostalgia that the physician surrenders what he regarded as a sharpened wit to the laboratory worker whose life is spent under so much more static a condition.

Saying this must in no way detract from the importance and usefulness of this study. Here the normal cerebral mechanism is computed and the variations wrought in this rate by anoxia, narcosis and such diseases as psychosis, mental deficiency and avitaminosis are estimated. These studies are of great practical interest to the clinician for whom they clarify the effect on the brain of anaesthesia and various therapeutic measures.

We should all try to understand the levels of function if we are to interpret properly the dysfunction which confronts us. A study of this book is a great help.

Ophthalmology By ARNO E. TOWN, M.D. Pp 511, with 208 illustrations and 4 coloured plates London Henry Kimpton 1951 Price 70s net

In the post-war years so many textbooks of ophthalmology have been produced that another is viewed with some critical interest. Professor Town's book is written for the undergraduate and the general practitioner and some sections have been contributed by colleagues.

The book includes sections on anatomy and physiology, optics, neuro-ophthalmology and medical ophthalmology and has interesting chapters on therapy and on "Standing Orders for Industrial Dispensaries."

Some aspects of ophthalmology are dealt with in considerable detail and the photographs and illustrations are outstandingly good. The section on glaucoma is disappointing. The early symptoms of this disease are of great importance to the general practitioner and, as the basis of the conduct of a case of glaucoma lies largely in the observation of the visual fields, this aspect could, with benefit, have received more space.

The book is thoroughly up to date in pathology and in treatment, and to the British reader the contemporary American view on ophthalmology is of interest.

A Synopsis of Ophthalmology By J. L. C. MARTIN-DOYLE, M.R.C.S., L.R.C.P., D.O. (OXON) Pp 246 Bristol John Wright & Sons 1951 Price 20s

This *Synopsis of Ophthalmology* is contained in a book of pocket size and is designed to meet the needs of the undergraduate, the general practitioner and the ophthalmic house surgeon working for a higher diploma in ophthalmology. The author has managed to include an amazing amount of information in little bulk and the references to recent work in ophthalmology serve to keep the general practitioner abreast of progress in the specialty. Not everyone will agree with many of the views held, but for its size this must be one of the best books of its type.

NEW EDITIONS

A Textbook of Medicine By RUSSELL L CECIL and ROBERT F LOEB Eighth Edition Pp xxxi+1627, with 204 figures and 40 tables London W B Saunders 1951 Price 60s

Textbooks in medicine are too numerous and some are too long and others too short, but this is a well laid out work covering every branch of internal medicine. Balance is maintained between competing interests, and it is obvious that all the contributors have worked loyally and co-operatively to a well thought out plan. No subject overrides the others. There are no unnecessarily long introductions nor weary tables of statistics but in each article the writer gets down to his subject and produces a clear and attractive account, which is complete and up to date. At the end of the article is a short list of references, mostly American. In spite of its many authors this is a well written book, more than adequate for students and suitable for post-graduates. The illustrations are of real value. The book is easy for reference.

Aids to Physiology By H DRYERRE, PH D, M R C S, M R C P, F R S E Fourth Edition Pp vii+327 London Baillière, Tindall & Cox 1951 Price 7s 6d net

A new edition of this small book has been produced after a lapse of nine years. Considerable alterations have been made to include the advances made in the interval, specially in biochemistry. It continues to act as a synopsis to supplement the standard textbooks.

Fractures and Joint Injuries By Sir REGINALD WATSON-JONES, B S C, M C H O R T H, F R C S, F R C A S, F A C S Fourth Edition In two volumes Vol I—Pp 470, with 709 illustrations Edinburgh E & S Livingstone Price (for two volumes) £6

The fourth edition of this world famous textbook has now started publication, the first volume being already on sale. Though the original format has been preserved little else has, since every chapter has been rewritten and many new ones added, along with some two hundred more illustrations. The new chapters include those on wound shock, the treatment of open fractures, control of infection, and a review of bone diseases that covers almost the whole of orthopaedic surgery. It will be seen that it overflows from the remit of its title, and no doubt Sir Reginald will develop his textbook till it really does contain everything an orthopaedic surgeon must know. One of the most interesting bits is the vigorous attack that is made on the belief that contact compression promotes union of fractures. We have always relied on the Liverpool School of Orthopaedic Surgery to do its share of debunking and are glad to know that this valuable faculty has been carried in the luggage to London. The various chapters are of such a uniformly high standard that it is invidious to select any for special mention. Transplantation of bone, with its wealth of beautiful illustrations, is particularly good and complete. Like other chapters it is the more interesting because of the historical background of the subject—much of it, one is proud to say, in Scotland. A happy change in this first volume is the inclusion of an index which, in previous editions, was only in the second volume.

The book is most beautifully produced, many of the illustrations being in colour, the first two, of H O Thomas and Sir Robert Jones, being delightfully reminiscent of the author's own consulting room. The volume is well up to the high standard expected from such an author and from such publishers. It is to be noted that the two volumes are not sold separately, but as a set, but who would want to buy only one!

BOOKS RECEIVED

- The American Rheumatism Association Rheumatic Diseases
(*W B Saunders Company, London*) 60s
- BEAUMONT, G E, M A, D M (OXON), F R C P, D P H (LOND), and DODDS,
E C, M V O, D S C, P H D, M D, F R C P, F R I C, F R S (EDIN), F R S
Recent Advances in Medicine Thirteenth Edition
(*J & A Churchill Ltd, London*) 27s 6d
- BLAND, JOHN H, M D The Clinical Use of Fluid and Electrolyte
(*W B Saunders Company*) 32s 6d
- CAMERON, GORDON ROY, M B, D S C (MELB), F R C P, F R S Pathology of
the Cell
(*Oliver & Boyd Ltd, Edinburgh*) £4, 4s net
- Edited by CONN, HOWARD F, M D Current Therapy, 1952
(*W B Saunders Company, London*) 55s
- CONYBEARE, SIR JOHN, K B E, M C, D M (OXON), F R C P, and MANN, W N,
M D (LOND), F R C P Textbook of Medicine Tenth Edition
(*E & S Livingstone Ltd, Edinburgh*) 37s 6d net
- Edited by DALEY, RAYMOND, M A, M D CAMB, M R C P, and MILLER,
HENRY, M D DURH, M R C P, D P M Progress in Clinical Medicine
Second Edition
(*J & A Churchill Ltd, London*) 30s net
- FROHSE, FRANZ and BRODEL, MAX Atlas of Human Anatomy
(*George Allen & Unwin Ltd, London*) 16s net
- GIRDLESTONE, G R, and SOMERVILLE, S W, M B, F R C S (ED) Tuber
culosis of Bone and Joint Second Edition
(*Oxford University Press, Toronto, Canada*) 45s net
- GLIDDEN, PAUL, and POWELL, MURIEL B Called to Serve
(*Hodder and Stoughton, London*) 7s 6d net
- GRISHMAN, ARTHUR, M D, and SCHERLIS, LEONARD, M D Spatial Vector
cardiography
(*W B Saunders Company, London*) 30s
- HOWORTH, M BECKETT, M D A Textbook of Orthopedics
(*W B Saunders Company, London*) 80s
- ISCHLONDSKY, N E, M D Brain Mechanisms in Coronary Disease
(*Henry Kimpton, London*) 25s net
- JOHNSTONE, R W, C B E, L L D, M A, M D, F R C S E, M R C P E, F R C O G,
F R S E A Textbook of Midwifery Fifteenth Edition
(*Adam & Charles Black, London*) 30s net
- JORDAN, EDWIN P, M D, and SHEPARD, WILLARD C B for Medical Writing
(*W B Saunders Company, London*) 12s 6d
- KLEINBERG, SAMUEL, M D Scoliosis Pathology, Etiology and Treatment
(*Bailhere, Tindall & Cox, London*) 57s 6d net
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M D Cardiac Emergencies and Heart Failure
(*Henry Kimpton, London*) 22s net
- MOYER, CARL A, M D Fluid Balance
(*The Year Book Publishers Inc, Chicago, U S A*) \$3 75
- Edited by OGILVIE, SIR HENEAGE, K B E, D M, M C H, F R C S, and THOMSON,
WILLIAM A R, M D Practical Procedures Second Edition
(*Eyre & Spottiswoode, London*) 25s net
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(*The Year Book Publishers, Inc*) \$7 00
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Edition
(*J & A Churchill Ltd, London*) 21s net
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(*The Williams & Wilkins Company, Baltimore, U S A*) £7, 10s net
- RODDIS, LOUIS H James Lind
(*Wm Heinemann, London*) 21s net
- WATTS, C A H, M D (DURH), D O B S T R C O G, and WATTS, B M, M B,
B S (DURH) Psychiatry in General Practice
(*J & A Churchill Ltd, London*) 12s 6d
- WHITE, FRANK D, A R T C, P H D (EDIN), F R I C, and DELORY, GEORGE E,
M S C, P H D (LOND) A Course in Practical Biochemistry Sixth Edition
(*J & A Churchill Ltd, London*) 17s 6d net

Edinburgh Medical Journal

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REFLECTIONS FROM A PROVINCIAL DEANERY

By J G McCRIE, OBE, TD, MB, FRCPE

Dean of the Faculty of Medicine, University of Sheffield

I THINK I need scarcely emphasise the honour which I feel it to have been invited to deliver a Honyman Gillespie lecture. In one respect I at first fancied myself to be more fortunate than some of the other speakers in the series must have been, for I thought that at least I should not find it difficult to avoid reference to the subject of animal experimentation. He would, I felt, be an ingenious man who, in exploring the subject with which I propose mainly to deal—namely, some aspects of Medical School administration—could devise a series of laboratory procedures designed to throw light on the problems connected therewith, intriguing and difficult though some of these problems undoubtedly are. Then it struck me that one of the reasons for my venturing to address you this evening at all is that I am somewhat in the position of being able to report upon an experiment. To explain myself, may I say that I wish first to offer some observations upon the nature of, and the functions attaching to, the Deanship of a Faculty of Medicine, with particular reference to the question of whether it is desirable, or undesirable, for such a Dean to be a full-time officer. Since the University of Sheffield was the first, and I think still remains the only, undergraduate Medical School both to decide upon such an appointment and to fill it with one who was previously a stranger to the School, I feel it is not incorrect to speak, in this connection, of an experiment. I hope I do not seem to be striking too personal a note. If I do, I can only plead that this seems to me to be, putting all personal questions aside, quite an important matter upon which those with an interest in medical administration may possibly find it useful to hear something, in relation to a policy whose desirability or otherwise is still the subject of quite widespread discussion. I shall try to be as objective as possible, and I should like to emphasise this point, since otherwise it might be thought that some of what I have to say was intended as criticism with a personal tinge. This is far from being the case. I am deeply appreciative of the way in which I, a newcomer into a post of a new type, have been received by my colleagues. It may be—it would be strange if it were not—that some of them hold views, which are different from my views, as to what constitutes the best and most convenient type of medical school administration, but I have never been conscious that this tinged their personal attitude.

A Honyman Gillespie Lecture delivered in Edinburgh, on Thursday, 14th December 1950

towards myself, and I trust I shall be believed when I say that the converse is—or at least that I earnestly try to make it—also true

The Goodenough Committee (1944) gave it as their opinion that “in most, possibly all, medical schools, it will soon become advantageous, if it is not already so, for the office of dean to be a whole-time (or almost whole-time) appointment” The reasons underlying this opinion—whether it be right or wrong—are not far to seek It has hitherto been the custom—and here one is speaking of University Faculties of Medicine, for such is not necessarily true of all Faculties in all Universities—for the holder of the office of Dean to be also a Professor, and, as such, the head of an important University Department It has also been usual—and here again we note a difference from other Faculties, especially in the English Provincial Universities—for the same person to hold the office over a considerable period of years I fancy most of us will think this sensible, and the Goodenough Committee “felt it to be open to question whether too frequent changes in the office of dean are in the best interests of a medical school” Since full-time clinical chairs are of comparatively recent development, it follows that the Dean has in the past usually been the head of a large non-clinical department (The Deans of the London Medical Schools are in a somewhat different case They are, of course, officers of their own Medical Schools, not officers of the University, consequently their time is chiefly devoted to School affairs, and they are, generally speaking, not greatly involved in general University matters The whole problem is somewhat different—(it is presumably because of this that the Deans of the London Schools are frequently practising clinicians)—and it is not proposed to deal further with it here In what follows I have in mind chiefly the Dean of a University Faculty of Medicine, as seen typically in the English Provinces and in Scotland) The amount of work which such a Dean must undertake has undergone an enormous increase of recent years Even the problem of student-selection alone has vastly increased In my own School, up to 1939, the applications for admission roughly balanced the number of places available, and the chief task in selection was to discourage the relatively small number of applicants who were clearly unsuitable Now we have, for each place, at least five applicants who must be seriously considered, apart altogether from the number who can be turned down on their paper applications While a large part of the work in this connection is clerical, and can be dealt with by enlarging sufficiently the Dean’s office staff, a not inconsiderable part of the burden must be shouldered by the Dean himself The National Health Service Act, too, has added to his responsibilities It is true that, in pre-NHS days, the Dean was frequently a member of the governing body of the teaching hospitals associated with his University, but the new Act, both explicitly and by implication, makes it necessary for University representatives to play an even larger part in hospital affairs, and the Dean of the Faculty of Medicine is a fairly obvious

choice for membership not only of the appropriate Regional Hospital Board and (in England) Board of Governors of the Teaching Hospital, but also of many of the Boards' most important committees. Nor does general University administration become any simpler. Staffs are larger, therefore there are more new appointments to be made, promotions to be considered, etc. Budgets reach astronomical figures, and require more time-consuming preparation. In all of these general University matters, it is to be presumed that, if the Faculty of Medicine is to be properly regarded within the University, the Dean of that Faculty must play his part. And, of course, the business of his own Faculty shares in the increased complexity. Apart from the general matters just referred to, new legislation brings new responsibilities. The assessing of house-posts as to their suitability for the period of internship prescribed by the new Medical Act will be a big initial task, and the collection of reports as to how the internships are performed, and the issuing of the necessary certificates, a permanent and continuing one. Then there is the whole problem of post-graduate education—from the operation of suitable schemes for the appointment and training of registrars, through the arranging of specialised diploma and other courses, to the working out and provision of the best types of instruction for general practitioners.

It will be admitted that this sort of burden is not one that can be carried over a long period by one individual, and yet leave him much time (even if it be in a supervisory rather than a personal capacity) for the teaching and research which are the prime duties of the Professorial Head of a University Department. Either, except in the case of an individual of exceptional gifts, he will have insufficient time to devote, personally, to his duties as Dean, or his departmental work—and probably in the first instance his research—will suffer. It seems a simple solution to say that in future Deans should be appointed as whole-time officers. Of course this *is* one solution, but I feel it worth while to glance at some of the disadvantages associated with it, and it may be convenient at the same time to suggest possible methods by which these disadvantages may be avoided or lessened.

Presumably the first disadvantage that may be felt to attach to a full-time Dean is that he is less easily got rid of than is one subject to periodic election—for I suppose it may be presumed that, once a full-time officer of the University is appointed, he is appointed *ad senectutem aut ad culpam*. With this goes the fear, on the part of those who distrust the idea of full-time Deanships, that the person appointed may forget the scriptural injunction "whosoever will be chief among you, let him be your servant," and may seek to make himself into a manager or dictator. This possibility is of course difficult to insure against, except by taking care over the appointment initially and by continuing vigilance on the part of the Dean's colleagues. It may, however, be noted that, while in many Universities the Dean is automatically regarded as Chairman of the Faculty Board, this is

not so in all. The *Oxford Dictionary* defines a Dean as a "President of a Faculty," and I think he is pretty generally accepted as such, in so far as his position in the general University hierarchy is concerned. But it does not follow that he is also Chairman of the Faculty Board, *z e* that he is in the Chair at what may be called business meetings. It is clear that, if *this is not so*, the opportunities for the Dean to force his opinions on the meeting are less. It would appear from such discussions as I have had with others—and these others comprise representatives of most of the English Provincial Universities—that each body thinks its own practice the best, some Faculties would never think of having the Dean in the Chair, others would regard anything else as impracticable. I mention the point because it does suggest a method of preventing a full-time Dean from becoming too assertive, and it is a method of procedure which many experienced University administrators say they find to work well in practice. Others, it must equally be emphasised, are against it on grounds either of general principle or of increased administrative complexity. I share this latter view, since I think that to have, as Chairman of the Faculty Board, someone other than the Dean suggests the use of the word "Dean" in the sense in which it is used in some (though not all) American Schools, *z e* that of "secretary" rather than "president." I should add that I speak with no sense of personal rancour, since, although in my own University we have now established the office of Chairman of the Faculty Board on an elective basis, as distinct from the full-time Deanship of the Faculty, my colleagues have done me the honour, in each of the last three years, of electing me to the Chairmanship in question.

My next point is a little more delicate. I presume that, when the Deanship is on an elective basis, the choice is usually made because of supposedly special gifts of administration and leadership in the person elected. But of course the choice is from among persons who have all already achieved the high degree of academic distinction or scientific prowess associated with occupancy of a Professorial Chair, and it is a question whether such distinction or prowess is not a *sine qua non* in one who aspires to be a Dean in the full sense referred to above—not only from the point of view of intra-Faculty relationships, but also having regard to the position which a Dean must occupy in the University as a whole, as, for instance, a member of the Senate. If so, the choice of candidates suitable for appointment to a full-time Deanship is obviously severely limited, since few teachers or researchers at the height of their powers would wish to retire from that particular field. There appear to be two solutions to the problem—to find a man of proved academic achievement who nevertheless, for some adequate reason, is desirous of transfer to the different, though not necessarily less exacting or interesting, field of administration, or, if making a selection from among candidates with a different background, to make that selection very carefully, and to be quite firm in the decision.

to make no appointment if no applicant considered to be of a suitable type presents himself

Another difficulty which is likely to arise when a non-Professorial Dean is appointed is a highly practical one, and that is the difficulty of his maintaining adequate contact with the student body. I use the word "adequate" deliberately, because the question is not one purely of degree. It is qualitative as well as quantitative. The student, naturally, regards the teacher whom he meets in the lecture theatre, the dissecting room, the morbid anatomy laboratory, or the hospital ward, with an affection and respect which is captured only with difficulty by the man who (the student thinks) does nothing but sit all day in an office. And of course the matter is quantitative as well, the full-time Dean just has not the physical opportunity to meet many students frequently. And yet his role in this respect, at any rate in the smaller Schools, has always been one of great importance, and I need not enlarge on its obvious potentialities in relation both to present morale and to the help he ought to be able to continue to extend to former students in their after-careers. This indeed is one of the great difficulties of the full-time Deanship. If the latter has become necessary because of the increase of administrative duties, it is this press of administrative work which itself renders contact with students so difficult. There is of course no solution which meets every case, but broadly speaking a remedy can be sought along two main lines: (i) by giving to the full-time Dean some small share in teaching work, and (ii) by the Dean himself doing all in his power to make contact with the undergraduate body through all other available channels. Under the first head, I do not feel that the instruction given by a full-time Dean can be in any of the main subjects, clinical or pre-clinical. He cannot possibly keep sufficiently up to date with these for him to feel any pride or confidence in the instruction he gives. Any form of "doctoring" is a 100 per cent job, not a 10 per cent one. But there are, I think, certain subjects which offer possibilities, *e.g.* the philosophic background to medicine (if the Dean's tastes and gifts lie in that direction), the history of the local Medical School (or Medical History in general, if he knows enough about it), medical ethics (if he has ever been a practising doctor), and so on. Under the second head, again personal tastes come in. I recently asked a very distinguished London Dean what the answer to this problem was. He replied that it was to be found on the football field. Since I myself intensely dislike any form of violent exertion, I cannot apply his remedy literally, but, as Sam Weller remarked, "hooroar for the principle". It is certainly most important for a full-time Dean not only deliberately to set aside regular times for the periodic interviewing of all his students, but also to be available when required for consultation on special problems, to take the Chair at student meetings, and generally to seek to make himself regarded as one interested in, and capable of playing a useful part in, undergraduate affairs.

The fact that I have devoted so much time to discussing the various ways in which the disadvantages of a full-time Deanship can be got over perhaps serves to emphasise that these disadvantages do in fact exist—which leads one to a consideration of the problem of whether the needs to which a full-time Deanship is one answer can be met in any other way. One obvious possibility, which has been the solution adopted by several Medical Schools for a number of years, is to put the day-to-day control of the Faculty Office under a Secretary or Senior Administrative Officer who is himself a medical man. There is no doubt that in this way a considerable burden can be lifted from the Dean's shoulders, for a great deal of the routine work can quite properly be undertaken by a Medical Secretary. At the decanal level itself, too, more sharing of duties than has been customary in the past is quite practicable. One obvious division, which in fact has already been made in many Schools, is to separate undergraduate from post-graduate affairs and to have both an "Undergraduate" Dean (who, by custom, still seems usually to be referred to as "the Dean") and a Post-graduate Dean or Director. There can be further sub-divisions within these spheres, as for instance when the (Undergraduate) Dean is supported by a Clinical Sub-Dean, whose sphere is implicit in his title, and sometimes by an Academic Sub-Dean as well. In the absence of a full-time Dean, such sub-divisions are necessary, for, even with a large part of the routine office work taken off the Dean's shoulders by a Medical Secretary, supported by an adequate clerical staff, there still remain a multitude of other duties which can properly be performed only by one who ranks as an Academic Officer rather than as a purely administrative official. One has in mind, for instance, the representation of the Faculty, or of the University itself, on important outside bodies and committees, where the representative may require to speak with more authority than would be possible in the case of the holder of a purely executive office.

It is really not my purpose to-night to recommend any particular procedure as the best. Obviously, different places and different circumstances call for different measures. I happen now to belong to a University where one particular policy has been adopted, and it is clearly for others, rather than for myself, to say whether or not it has been a success. I do, however, feel that it may be useful to those who may have to consider this problem in other places or at other times to hear something of the question as viewed from one particular angle. I think quite a good case can be argued that, for various reasons which have been indicated above—and doubtless for others also—it is wise to retain the old idea of a part-time Deanship on an elective basis. In this case, a good deal of devolution will be required even at what may be called the "policy" level, and the various duties which it has in the past been customary for the Dean to undertake in person will have to be shared among an increasing number of his colleagues. In addition, the routine administrative

side will require considerable strengthening, this including (where such an arrangement does not exist already) putting the office side in the charge of a medically qualified individual who will undertake much of what were formerly regarded as decanal duties, such as the interviewing of prospective students and their parents, disciplinary work except in really severe cases, and so on. I may say that, from some personal experience, I regard this arrangement as not at all a bad one. It preserves many of the advantages of the old system, and avoids some of the difficulties of the new. It is true that I personally would prefer to be a Dean than to be a Medical Secretary, and that fortune has favoured me in enabling me to undergo such a metamorphosis, but, looking at the question objectively, I can see many advantages in the system just outlined. On the other hand, "it's an ill bird that fyles its ain nest," and I certainly do not want to be understood as condemning the alternative system—the full-time Deanship. It has many administrative conveniences, it fits well into modern University and hospital organisation, and, always given the necessary compatibilities of personality, it can be made to work satisfactorily. I should naturally hesitate to say—because it is clearly for others, and not for me, to make the judgment—that that has been proved in my own School, but there are after all other Schools that have made comparable experiments and apparently found them satisfactory. I feel that I have discharged my duty in this respect to-night if I merely sketch the possibilities, and leave it to others to make the choice between them. I do feel, however, that it is important for any School considering the possibility of appointing a full-time Dean to make up its mind fully that this is genuinely what it means, and that it does not have the intention of merely giving an imposing title to someone whom it visualises, and really means to treat, as a sort of administrative and clerical hack. I would add that it should be obvious from what I have already said that I speak with no personal sense of grievance in this matter, but merely because I see the obvious difficulties and frustrations which might arise had this matter not been very carefully weighed and sifted beforehand, and a firm and binding decision been taken with regard to it.

Of the various problems to which the Dean, or other administrative authority, of a Medical School must devote a good deal of his attention, that of the selection of students for entry to the School is one of the most urgent and time-consuming. Unfortunately it is also, for reasons which will be discussed below, one of the most unsatisfactory. Of the urgency of the task, and also of its magnitude, there can be no doubt, for, whatever be the number of places available in the School, it is certain that the number of applicants will be far in excess of this. As to the reasons underlying the phenomenal increase in numbers which has taken place within the last few years there is perhaps little point in arguing, since the situation, whatever the reasons for it may be, is simply one which has got to be faced up to, and dealt with on

whatever lines appear to be the most rational to the authorities of the particular School concerned. Among factors which have been suggested, however, there may be mentioned (Roberts, 1948) social ambition, the call of idealism, the lowering of financial barriers, and the search for economic security. I think there is little doubt that both the first and the last of these are factors of considerable importance at the present time, though whether they will continue to be so under the conditions introduced by the National Health Service Act remains to be seen. The actual reality and practical effect of the second factor mentioned—the call of social idealism—is difficult to estimate when one is dealing with the particular age-group in question, that is before personality and interests are fully moulded. While I certainly feel that social idealism, or a sense of vocation, are operative factors in a small proportion of cases even at this stage, I see too many applicants who have already made up their minds to be plastic surgeons, psychiatrists, or (rather surprisingly) gynæcologists, to take this very seriously in most cases. Taken all in all, it would seem that the most important factor—and indeed that which has in large part allowed the others to become operative—is the lowering of those financial barriers which, even at the time of the Goodenough Report, were reckoned to play an important part in preventing the recruitment of some of the ablest students into the Universities. To those unconnected with University administration it may, I think, come as a surprise to learn how profound is the social change which has come about in this regard. Even in 1946, when I myself first became immediately concerned with the problem of student selection, it was impressed on one that it was necessary to make careful inquiry into an applicant's financial background—not, of course, that this was to be a major factor, in the average case, in determining his suitability or otherwise for admission, but simply because it had been found as a matter of practical politics that, if suitable enquiries were *not* made in appropriate cases, difficult situations were apt to arise if it became apparent, in the later years of a student's course, that his parents had allowed him to embark on a career which they were in fact not financially able to permit him to complete. Nowadays, the scale of State and Local Authority aid available to the majority of students who qualify on academic grounds for admission to a University Medical School is such that I rarely, at the time of selection, give attention to this aspect of things at all, and I can think of few cases in which trouble has resulted. Some simple figures may be illuminating in this regard. I have divided the students of the Sheffield Medical School, for the Sessions 1938-39 and 1950-51 respectively, into two broad groups—(a) “receiving financial assistance” and (b) “self-supporting”. The line of demarcation is of course not sharp, while the fact that some of the relevant data are of a confidential nature also complicates the investigation. Thus, some of the “self-supporting” group may have a relatively small grant, scholarship, or loan, while in the “financially

assisted" group no distinction is made between those in whose case the assistance covers fees only and those who receive also maintenance grants. I think, however, there is little doubt that nowadays the payment of fees from public funds is in most cases accompanied also by a maintenance grant. In any case, the broad distinction is between (a) those in receipt of substantial financial assistance and (b) those predominantly self-supporting. In Session 1938-39, of a total of 172 students, 14 (8.1 per cent) fell into group (a) and 158 (91.9 per cent) into group (b). In respect of Session 1950-51, the position is largely reversed. Of a total of 348 students, 266 (76.4 per cent) are in group (a) and only 82 (23.6 per cent) in group (b). It seems to me that it is probably unnecessary to look very much further for an explanation of the greatly increased numbers of applicants who are now seeking admission to Medical Schools. What these numbers actually are is still a matter of some doubt, since the pressure of competition leads many, probably most, applicants to apply to more than one Medical School. Part of the M.R.C. investigation (Harris, 1948), to which further reference will be made below, is designed to elucidate this particular aspect of the problem—not only because, as Harris points out, an increased number of applications might be due either to more people applying or to the same number of people making more applications (while, equally, a fall in the number of applicants might be concealed by this factor of multiple application), but also because it is of great importance for research purposes to know accurately the total number of applicants to Medical Schools, since the proportion between applicants and places available plays a considerable part in determining the type of selection methods which are likely to be appropriate. Whatever be the upshot of this investigation, the fact remains that all Medical Schools are now confronted with a mass of applications vastly in excess of the number of places available—the ratio of applicants to available places being said to be, in some medical schools, as much as 20:1—and the brutal and practical issue must be faced year by year of selecting, from among this mass of applicants, those who are actually to be offered one of the available places. I use the word "offered" advisedly, for one of the complications of the present "multiple application" system is that, when after infinite consideration and labour the offers of places are finally sent out, a variable proportion of refusals is received, from those who have already been accepted elsewhere but who have failed to notify this fact to the numerous other Schools to whom application has also been made. And so the process continues until, perhaps even after the session has actually started, the last place is eventually filled. Some Schools have sought to overcome this difficulty by such means as the charging of "application fees," "reservation fees," etc., or by getting accepted candidates to sign a statement that they have withdrawn all other applications. But it seems clear that none of these methods is a real solution to the problem, and some of us, after trial, have

abandoned them, since the extra labour involved did not appear to be justified by the results. From time to time the idea has been mooted of some sort of Central Registry to which all applicants would send in their names, at the same time indicating in order their preference for the various individual Schools. The central organisation would then arrange, after discussion with the Schools taking part in the scheme, for such interviewing of candidates or other means of selection as might be decided upon, and ultimately furnish each School with a list of those students who had been allotted to it. This would seem to provide the only real and lasting relief from the difficulties arising from multiple applications, but it is clear that the very great practical difficulties in creating and operating such an organisation could be overcome only if it had the enthusiastic support of all (or at least most of) the Universities and Medical Schools. And this at present seems unlikely to be forthcoming, in the succinct words of a leading article in *The Lancet* (1948), "rightly insisting on freedom in selection, they (*i.e.* the Universities) often fear that such a device, though voluntary at first, might soon become mandatory, and that central registration would lead to central allocation."

It would appear therefore that there is no hope of early release, so far as most Medical Schools are concerned, from the large and difficult problem which confronts them each year of making what they consider to be an appropriate selection from among the huge number of applicants who desire to enter, and the difficulty of course centres round the problem of what constitutes the basis of "appropriate selection." As has been remarked, "if we have no basis at all, the proper thing would be to throw all the names into a hat and draw out the appropriate number." But the not unreasonable belief persists that there must be some basis better than that of pure chance, and it is the search for this basis which constitutes the core of the problem. The initial difficulty is to define exactly what it is that we are looking for in our medical students. There is general agreement (Goodenough Report, 1944) that the over-riding factor in selection ought to be "promise of developing into a good doctor." But what in fact do we mean by a "good doctor," what are the qualities which give promise of such development, and how are they to be measured? A certain level of intelligence is of course important, for it is obvious that, unless a student can first clear the hurdles presented by the medical course and its associated examinations, he can never arrive at the point of beginning the actual practice of his profession, admitted though it be that, in such practice, certain qualities may be much more important than that of pure intelligence—such qualities as, for instance, intellectual honesty, a high moral standard, and willingness to sacrifice personal interest for that of others, together with gifts (Layton, 1948) of a more subtle nature—"the kindly heart, the gentle touch, the control to keep a confidence, the love of children, with the power to make a decision and to accept responsibility." It is clear that a great deal

more investigation is called for into what constitutes "a good doctor" Millar (1948) has suggested the undertaking of a "job-analysis" in relation to doctoring. He agrees that it would be a very big task, but considers it could usefully be done. Others have felt, on the contrary, that, so complex is the business of doctoring, so manifold the characteristics that lead to its being practised well or ill, and indeed so many the different types of career that may be comprised within it, it would defy job-analysis in the ordinary sense, and that empirical studies are more likely to lead to useful results than are methods which at first sight would seem more rational. Among the methods which, as has just been said, would appear at first sight to be more rational, are those which are often rather vaguely referred to as "psychological methods of selection". It may, however, be remarked that the most urgent suggestions for the use of such methods come from those whose acquaintance with the use of them is least extensive, or rather, to put it the other way round, that those with the most exact knowledge of, and the greatest experience of, such methods are precisely those who at present advise caution in their use, or at least emphasise that the most urgent requirement at the present time is not the introduction of new methods as actual modes of selection, but rather the initiation of really long-term experiments whereby certain data can be collected by appropriate tests, and these data then be checked against the subsequent careers of the persons originally examined.

It is satisfactory to know that certain long-term investigations of this type have already been initiated. University College, London, was early in the field in this regard, and Smyth's paper (1946), and Bartlett's comments upon it, form a valuable introduction to the problem. The Nuffield Foundation, more recently, has launched an experiment designed to last some eight to ten years, whereby an appropriate series of objective tests will be applied to all (not only medical) students seeking entrance to certain selected Universities, further tests of those accepted will be carried out during their University career, follow-up studies will be made of all of these as well as of (so far as possible) those applicants who were not in fact successful in gaining admission, and the question will in due course be investigated of whether or not any correlation exists between the results obtained in the tests applied and "success" at the University and in after-life. The tests are designed to cover not only intelligence, but also qualities falling within the domain of character, temperament, and personality. The potential value of such an investigation is obvious. It is probably generally accepted even at the present time that appropriate intelligence tests can be of value in eliminating those who clearly do not possess the necessary intelligence for a medical career, and therefore that such tests can be of value to selectors in helping to eliminate obviously unsuitable applicants, and therefore in making more time available for the consideration of those not so eliminated. But this is probably as far as the matter has gone up to now. Intelligence testing is

valuable where rapid separation over a wide range of talents is desired, but is of much less help in discriminating between members of a group the majority of whom occupy the upper end of the scale. This is, however, a highly technical matter which I myself am not competent to pursue further. Besides, as already remarked, a great deal more than intelligence goes to the making of a good doctor, or even of a good student. Determination, stability, adjustability to changing situations—all of these may be far more important. And the investigation to which I have referred is designed to discover whether objective methods exist, or may be devised, to measure qualities such as these, and to find to what extent these correlate, or otherwise, with success in the chosen profession. I am particularly interested in this matter, since the University of Sheffield is one of the centres chosen by the Nuffield investigators for their work. I must, however, emphasise that the investigation is purely a test of tests, and in no way a test of students. The University authorities, although they on their side furnish (under conditions designed to preserve anonymity of the students concerned) certain information asked for by the investigators, have no knowledge of what views the latter are forming in relation to any individual, and the investigation plays no part in the University's own selection of students or in the subsequent treatment of those admitted. The two procedures are running in parallel, and it will not be for a period of years that it will be known whether the two have been found to correlate, and, if so, how far. It is particularly important that this should be appreciated, not only because it is clearly the only reasonable attitude to be taken towards an investigation whose object is to establish the validity, or invalidity, of certain procedures, but because the students themselves must be made to realise this in order to avoid on the one hand their deliberately refusing to take part in the investigation, and on the other hand their indulging in some sort of cramming or coaching beforehand, although I understand the tests are so designed as to minimise this latter effect as much as possible.

The investigation which I take to be along similar lines, but restricted to medical students, that is at present being conducted by the Medical Research Council, has been described by Harris (1948). Naturally we should have been greatly interested to co-operate in this, but, our Nuffield programme having been already launched, we felt we had reached the limit to the number of voluntary procedures to which we could properly ask our students to submit—though in this respect it is interesting to note the opinion recorded by Harris that “the willingness of medical students to submit to interviews and tests, administered by some ‘snooper’ from outside, is a great tribute to their long-suffering”.

The results of the Aberdeen experiment (Millar, 1948) will also be watched with interest, although I understand (personal communication) that its commencement has had for various reasons to be postponed beyond the expected date. Here, it is proposed, by means of a comprehensive series of procedures based in general on

War Office Selection Board methods, to gain as much relevant information as possible about each first-year student and to check this against his subsequent performance in the University and perhaps beyond

It seems that, in the long term, much interesting information should become available to us as a result of the investigations described. It may be that it will be information which is practical and useful in the sense of indicating that there are objective and scientific methods which could justifiably replace, or at least supplement, the empirical and personal methods on which we are at present forced to rely in the selection of our students, or it may be information which points in precisely the reverse direction, or it may be indecisive. But at any rate it will be good to know. It is because we are at present working so much in the dark that, in beginning to discuss this question of student-selection, I referred to it as an "unsatisfactory" task. It is of course clear that, as regards the really long-term experiment, one of the difficulties will be the selection of the criteria of "success," in respect of which we are going to evaluate the data obtained at an earlier stage. At least, however, in the case of a man's undergraduate career, such criteria should be reasonably clear, and, even if all we felt was that we could reasonably prognosticate which applicant would complete his student career satisfactorily and which would not, much would have been achieved. If the matter can be carried further, so much the better. At present, as Harris (1948) points out, we have advanced little beyond the study made by Sir James Paget in 1869. He found that, of 1000 students traced by him, 23 had achieved distinguished success, 66 considerable success, 507 fair success, 124 very limited success, and 56 had failed entirely, while 41 had died during pupillage, 87 within twelve years of starting practice, and 96 had left the profession. The range of talent was exhibited by the fact that the series covered three Professors of Anatomy (Oxford, Cambridge, and Edinburgh), and, at the other end of the scale, two men who had committed suicide under circumstances of great disgrace, together with Palmer, the Rugeley murderer, who was hanged.

Pending such accurate information as we hope may, in due course, be forthcoming, it may be of interest if I make, briefly, a few observations on such selection methods as are at present available and commonly made use of —

I find a fairly full type of application form to be desirable—one giving not only basic information, but also some account of the applicant's interests, hobbies and recreations. This is not only useful in the preliminary screening of the written applications, but saves time at interview. At the latter, however, care must be taken to check the genuineness of the entries, the range of a candidate's real interests often fall far short of what he has professed on paper¹. A small photograph attached to the form is most helpful in bringing the individual back to mind when his application is looked at perhaps some time after interview.

Naturally a headmaster's report is always given careful attention, though one's attitude towards it must vary somewhat according to whether or not one knows the headmaster in question, or has considerable previous experience of his reports (as, for instance, in the case of local schools). This difficulty, incidentally, might be cited as an argument for having a not too rapidly changing panel of selectors, or for having a permanent chairman of that body (as for example the Dean) who over the years comes to know the characteristics of different headmasters.

The question of the applicant's educational background, academic record, and previous examinational achievements, is obviously an important, and at the same time a somewhat controversial one. There is of course frequently the practical difficulty that the candidate is sitting some examination (such as, in the past, the Higher School Certificate) in the Session just preceding that in respect of which admission to the University is sought, and the results of this may not be available at the time when the applicant is interviewed. In my own Selection Committee the understanding is, in these circumstances, that we rate the candidate on the assumption of an "average" performance in the examination in question, and that I as Dean am given general authority later somewhat to raise, or somewhat to lower, the rating on the strength of an exceptionally good, or an exceptionally poor, examinational performance. But of course far more fundamental questions arise in this connection—first, what regard is in general to be paid, in rating a candidate, to apparent examinational ability as opposed to other factors (so far as these can be judged) such as character, temperament, aptitude for a medical career, etc., and second, what kind of educational background is desirable in our future doctors. As regards the first of these questions, I suppose that there would be general agreement only on the principle that really poor examinational performance at school should probably be regarded as a contraindication to admission. (It may be objected that *all* candidates who can be considered must at least have satisfied University entrance requirements, and that it is odd to describe such a performance as "really poor".) Nevertheless, so great is the competition for places nowadays that nearly all candidates have more than the bare minimum, and many have much more, and I think it would be unfair to the majority to regard only minimal attainments as, for this purpose, other than poor.) Much more debatable is the question of whether only average academic attainments combined with apparently the right qualities of character and temperament should be rated as higher or lower than outstanding examinational ability combined with what (in the view of the selectors) are less good qualities in other directions. It is of course because of the difficulties in this connection that the whole question of objective procedures in relation to student selection is, as has been indicated above, being so actively explored. Few, I suppose, would deny that examinational ability is not the chief factor that goes to the making of a good doctor, and that, given the necessary

ability to pass the necessary examinations at the different stages of the medical course, other qualities in the applicant may be far more important. But few, on the other hand, would be prepared too lightly to abandon the objective measure of reasonable examinations in favour of subjective procedures in which, unless the selectors be both skilful and conscientious, there is a real danger that mere "likeability" may obscure more significant factors. The second question, that of the educational background which we would consider desirable in our medical students, is equally debatable. It probably assumes more importance in England, where "First M B exemption" obtained at school bulks so largely in the educational system, than it does in Scotland, where the First M B course and examination are, in normal circumstances, intramural so far as the University is concerned. The disquiet which is felt in many quarters in relation to this matter was expressed at a recent meeting of the Royal Society of Medicine (1950). It was there pointed out by the Headmaster of Eton that at some English Medical Schools it is now almost a prerequisite for admission that the student should first have obtained "First M B exemption", it following as a result that the boy intending to pursue a medical career often had, after the age of fifteen to sixteen, no instruction except in physics, chemistry, and biology. This was educationally unsound and indefensible, particularly in view of (as most would suppose) the value of a general cultural background in relation to the practice of medicine. These remarks assume a particular pertinence when viewed in conjunction with figures published by Johnson (1949). This observer pointed out that, of students admitted to pre-clinical studies in University College, London, only one-fifth to one-quarter have taken the internal course at the College leading to First M B exemption, the remainder have obtained this exemption externally. The UCL selection procedure leading to admission to Second M B courses is very stringent, it is based on the applicant's school record, his performance at a special entrance examination, and interview by a selection board, and the ratio of applications to admissions is about 7:1. Yet, of 41 applicants who in 1948 were offered Second M B places subject to their first obtaining First M B exemption, 18 (i.e. more than one-third) failed in this latter requirement—and one of the 18 had been considered by the selection board to be the most outstanding man interviewed, and had obtained the third highest mark in the special College entrance examination. It seems to me that there are good grounds for holding that the tendency which has been so largely followed in England, of supposing the best preparation for a medical course to be early specialisation at school in chemistry, physics, and biology, is a mistaken one. On the other hand, I think it would be wrong to underestimate the difficulty, to the student of limited or only average ability, of completing the whole First M B course in the University in one session unless he has *some* previous knowledge of at least chemistry and physics. In Sheffield, we are so placed as to make it desirable to allow First M B exemption, and

direct entry upon Second Year courses, to a limited number of students, and I do not question this policy in appropriate and selected cases. But speaking in general terms, I think it wiser educationally for First Year studies to be carried out within the Universities, for the school curriculum leading up to this to have been as broadly-based as possible, but to have included chemistry and physics up to at least the old School Certificate "credit" standard, with the understanding that this latter proviso can be abrogated in the case of those whose examinational performance in other subjects shows them to be of such exceptional ability as probably to be able to achieve success in the First M B after only one session's work in spite of the handicap imposed by lack of any previous knowledge of the subjects in question. I should add that I am impressed by the procedure in vogue at Liverpool whereby it is sought to mitigate the effects of undue specialisation at school by allowing students who have already passed one, or two, of the First M B subjects (and, I think I am right in saying, even some of those students who have complete "First M B exemption") to enter only the First Year at the University, but there to require them to take only the First M B subject or subjects in which they are lacking, and meantime to allow them to attend, without fee, any other classes in any Faculty which they may choose. The eight-term pre-clinical course now under consideration by London University (*Lancet*, 1950) is also a move away from too early specialisation. It will (personal communication) abolish "First M B exemption" on school work, the whole eight-term course leading up to Second M B—an integrated one in chemistry, physics, biology, anatomy and physiology—having to be taken intramurally. It is true that some previous knowledge of chemistry and physics will be required of the entrants, but only up to Ordinary standard in the new General Certificate of Education, so that there is room for a considerable spread of other subjects at school.

This brings me to the last of my sub-heads in relation to the subject of student-selection, namely the interview. Most Medical Schools (including my own) regard this as a *sine qua non*, although we are of course prepared to make certain concessions in regard to a small number of applicants from overseas whose suitability appears to be guaranteed by other means. It is likely that this (i.e. the importance attached to personal interview) will continue. As Harris (1948) aptly remarks, "it is as unlikely that any development in testing practice will supersede it as that laboratory aids to diagnosis will supersede the clinical examination of patients." The role of the interview has already been touched on in discussing the importance to be attached to an applicant's previous examinational achievements, for it is at the interview that the final attempt is made to synthesise all the available information—what the candidate says about himself in his application form, his Headmaster's report, such examination results as are available, and what can be learned at the interview itself about the applicant's character, personality, temperament, sense of vocation, etc.—and as a

result to give him the rating which will determine his place upon a list and ultimately his chance of acceptance or otherwise. It is usual, I think, for such interviews to be conducted by small committees—consisting of say, three—selected for each day from a panel of a larger number. It is obviously advisable for the Chairman to be one who attends all, or at least most, of the interviews, in order to ensure as far as possible uniformity of procedure and of standard. The chief difficulty, as has already been indicated, is to secure agreement as to the degree of weight to be attached to the various factors considered. There can obviously be no finality about this at present. That must await the outcome of the various investigations into selection-procedure already described, and of course it is quite likely that there may be no finality even then. Still, it is remarkable how much agreement there is, among those who have given considerable thought to this problem, as to how often what appear to be quite reasonable results are arrived at by present methods, possibly because in most Schools there usually seem to be one or more individuals who have what can only be described as a “flair” for this kind of work. As Harris (1948) says, “it is unpopular to speak of any form of individual judgment as a reliable instrument, but it seems to me that there can be little doubt that it is sometimes not only reliable but amazingly sensitive.” Smyth (1946) has stressed the importance to a School of identifying persons gifted in this way.

It would seem that continuance along present lines is all that can be done until much more information is available about the value of other possible methods. It is, of course, quite likely that all we can really do at present is to pick out, on the one hand, those applicants whom we are almost certainly right to take, and, on the other hand, those whom we are almost certainly right to reject. With the number of places available in most Schools, this usually leaves an intermediate zone of varying size in different years. So far as the applicants in this zone are concerned, it would probably make little difference if, instead of going through the whole procedure, one simply put the names into a hat and drew out the appropriate number, but of course we cannot know which applicants *are* in fact in this zone unless we have completed the whole procedure in respect of all the applicants whom we want to consider at all.

There remains one final point to which, in conclusion, I should like to refer. There is an almost universal feeling that, in addition to whatever methods we may adopt in relation to initial selection, there should be a fairly ruthless “weeding-out” of those students who fail to make satisfactory progress in the earlier stages of their University career. Certainly it would appear humane that, if a student is going to be in the end invited to discontinue his studies, that invitation should be conveyed to him before he has wasted too much time upon such studies—that is, at the end of the First M B stage, or certainly no later than that of the Second M B. Although I of course see the reasonableness of this argument, I sometimes wonder

if we are on really sure ground here Does performance in the earlier examinations really correlate well with that in the later? Put more bluntly, is difficulty over chemistry or physics really incompatible with success in clinical work and the academic subjects studied therewith? One may feel specially doubtful about this in view of Johnson's (1949) remarks, already quoted, in relation to the First M B On the other hand, as Johnson has himself agreed, the circumstances of the "external" First M B are rather special, and although data correlating internal First M B results with later achievements are scanty, we have at least the finding of Gibson (1948) in relation to the (internal) First M B at Belfast This observer found that, of those who completed the First M B at the first attempt, most proceeded directly to qualification, whereas most of those who completed it piecemeal failed again later in the course Though Gibson is careful to point out that it has not yet been shown how performance as a student correlates with performance as a doctor, it is comforting to realise that there is at any rate some objective justification for "weeding out" in the early stages

I had originally supposed that, in these random reflections from a Provincial Deanery, I should cover a wider field than I have in fact done, for it must not be thought that my energies are entirely devoted to wondering, in the first place, whether I ought to exist at all, and in the second place whether we are going about our selection of students in the best way There are of course many other problems at which it might have been profitable to glance, but I fear that time will not permit of that being done to-night I confess that I feel somewhat humbled in looking at the list of the titles of the lectures that have already been given in this series There seem to be so many people who know so much about such intricate subjects that it gives one the feeling of being—how shall I put it?—rather a dunce among the learned I can only hope that something which is, I think, a little off the usual lines, and presented by a worker in rather a different field, may perhaps have been not without interest to some of my hearers

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THIRTY YEARS' EXPERIENCE OF THE MEGALOBlastic ANÆMIAS

By L S P DAVIDSON, B A Cantab, M D, F R C P E, and Lond

(From the Department of Medicine, University of Edinburgh)

DURING the past eighteen months, many discussions have taken place at medical societies and many reports have appeared in the medical press about the roles of vitamin B₁₂, folic acid and folinic acid in the maintenance of normal hæmatopoiesis and the mechanisms and pathways by which they subserve this purpose through their influence on the metabolism of nucleic acid. I believe it is true to state that any opinions expressed on these matters at the present time are largely hypothetical, as information based on acceptable data is still insufficient to warrant the formulation of any definite conclusions. Accordingly, I do not propose to deal with this aspect of the pathogenesis of the megaloblastic anæmias but shall utilise the short time allotted to me for discussing a few personal impressions and experiences of a group of anæmias with which I have been interested and intrigued for a period of more than thirty years*.

My experience of hæmatology falls naturally into three periods. The first covers my work in Edinburgh during the years 1919-29, the second my occupancy of the Regius Chair of Medicine in Aberdeen from 1930-38, and the third occupies my term of office as Professor of Medicine in the University of Edinburgh from the time of my return to that city in October 1938 until the present time.

PERIOD 1, EDINBURGH, 1919-29

It was my good fortune as a young doctor to be successively Assistant, Clinical Tutor and Assistant Physician, first with Professor Gulland and later with Dr Goodall, who during that period were the leading hæmatologists in Great Britain. It is, therefore, not surprising that I became interested in this speciality at an early age. The particular aspect of this period which I should like to discuss briefly is the difference which I have noted in the clinical picture of the cases of pernicious anæmia seen by me in the wards of the Royal Infirmary in Edinburgh prior to 1927 as compared with the patients in my wards in Edinburgh in 1951. Between 1919 and 1926, when the discovery of liver therapy was announced, I had the opportunity of studying the clinical features and watching the course of many cases of pernicious anæmia in Professor Gulland's wards until they reached their fatal termination. The description of the disease in many textbooks of

* This paper is based on a lecture on the megaloblastic anæmics delivered to the Royal Society of Medicine.

medicine in use to-day is still largely based on the clinical picture seen before the introduction of liver therapy. The failure to appreciate the fact that many clinical features, formerly held to be of great diagnostic value are rarely encountered to-day, is a potent cause of delay in diagnosis and the institution of proper treatment. Last year I asked Dr Newall, one of my Assistants, to examine the case records and classify the clinical features of a consecutive series of 135 cases of pernicious anæmia seen at my Blood Clinic during the period 1944-48, and compare them with any reports that he could find in the literature of the clinical features as they existed prior to 1925. The following information obtained from Dr Newall's analysis and from my own experience may therefore be of some interest.

Age of Onset—More patients are apparently developing the disease in older age groups nowadays than they did fifty years ago. Thus the onset of the disease occurred between the age of sixty and eighty years in no less than 42 per cent of our cases seen during the period 1944-48, as compared with 18 per cent of the 110 cases reported by Cabot in 1900.

Another point of interest investigated by Dr Newall was the *duration of the disease before the patients were referred for a hæmatological opinion*. It was found that 37 per cent of our recent patients had had symptoms for three months or less, 70 per cent for six months or less and 80 per cent for twelve months or less before being referred to our Blood Clinic. In contrast, Panton (1923) stated that the average duration of symptoms before obtaining a hæmatological opinion was fourteen months. It is obvious that early diagnosis will be an important factor in influencing the accepted clinical picture of pernicious

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Glossitis—Prior to 1927 the majority of patients dying of pernicious anæmia in Professor Gulland's wards had acute glossitis as indicated by the fiery red colour of the tongue and the presence of ulceration. These appearances were seen in about 5 per cent of our recent series of 135 cases. On the other hand, a smooth atrophic tongue was present in approximately 80 per cent of these cases. It should be pointed out that the features of atrophic glossitis in pernicious anæmia are indistinguishable from the changes in the tongue which are frequently seen in women suffering from chronic nutritional iron-deficiency anæmia.

Diarrhœa for which no obvious cause can be found was a very characteristic feature of pernicious anæmia twenty-five years ago. In our recent series, diarrhœa occurred in only about 10 per cent of cases in contrast to the incidence of 30 and 40 per cent mentioned in the reports of Panton in 1923 and Cabot in 1900 respectively. Our case notes suggest that constipation occurred twice as frequently as diarrhœa, while minor alimentary upsets such as mild anorexia, dyspepsia or flatulence were commonly noted.

Clinical Jaundice, which was present in nearly every patient dying

of pernicious anæmia twenty-five years ago and on which so much stress was laid as a diagnostic feature, is very much less frequently encountered to-day. Jaundice seldom becomes obvious until the red-cell count has fallen below $1\frac{1}{2}$ millions, hence its presence is an indication that diagnosis has been regrettably delayed either because the practitioner has been incorrectly educated in regard to its clinical significance or else because insufficient hæmatological facilities are available to him in the region in which he works.

Ataxia.—In contrast to twenty-five years ago, when ataxia was a common presenting complaint, it was rarely noted in the series seen in Edinburgh during 1944-48. Only one patient out of 135 stated that the reason why he initially consulted his doctor was because of unsteadiness on walking. Signs suggestive of involvement of the posterior columns of the spinal cord were found in approximately 10 per cent of cases, although a complaint of subjective sensations such as numbness and tingling in the limbs was made by one out of every three patients.

Splenomegaly.—In my experience of the disease prior to 1927, a palpably enlarged spleen was present in at least 30 per cent of cases, while in our series of cases recently investigated in Edinburgh the spleen could be felt in less than 10 per cent of cases. The enlargement, when present, was only moderate in degree and could usually only be detected on deep respiration.

Sufficient has been said to make it clear that the clinical picture of the disease, so frequently seen prior to the discovery of liver extract, as indicated by clinical jaundice, acute glossitis, diarrhœa, ataxia and splenomegaly, can no longer be accepted as being satisfactory if early diagnosis is to be achieved and adequate treatment instituted before the development of serious complications (see Table I). The main presenting features seen in cases of pernicious anæmia at the present time are weakness, dyspnœa on effort, vague dyspepsia, pallor of the skin and especially of the mucous membranes. It should be stressed in textbooks of medicine that the diagnosis of pernicious anæmia cannot be made solely by physical examination or on the presenting features of the disease, since these are not pathognomonic of any particular type of anæmia. A competent hæmatological examination is the only method which will enable the correct diagnosis to be made.

The second impression of this period which will ever remain vividly in my memory is the thrill which I got from treating my first case of pernicious anæmia with liver in 1927. Only those who have watched the inevitable progress of this fearful disease to its fatal termination prior to the introduction of liver therapy, can appreciate the amazement and delight with which we noted the extraordinary change in the patient's sense of well being and the return of a pink colour to the pallid lemon-yellow face which occurred within a few days of the commencement of treatment. Twenty-five years ago there were no hæmatological technicians in the Royal Infirmary, Edinburgh, and

accordingly at that time, and for many years after, I had to undertake all necessary blood investigations myself. This at least gave me the great personal satisfaction of observing for the first time the dramatic rise in the reticulocyte count which commenced about the fifth day of

TABLE I

The Clinical Features of Pernicious Anæmia Prior to 1927 and After 1944

	Edinburgh 135 cases (1944-48)	Cabot 110 cases (1900)
Percentage of patients aged over 60 years at onset	42%	18%
Duration of symptoms before the patient was submitted for a hæmatological opinion	Under 3 months—37% Under 6 months—70% Under 12 months—80%	Panton (1923) average duration 17 months
CLINICAL FEATURES		
Acute glossitis (red ulcerated tongue)	5%	Edinburgh (prior to 1927) very common
Chronic atrophic glossitis (pale smooth tongue)	80%	==
Diarrhœa	Less than 10%	Edinburgh (prior to 1927) very common Panton (1923)—30% Cabot (1900)—40%
Clinical jaundice	Uncommon	Edinburgh (prior to 1927) very common
Involvement of C N S	Less than 10%	Edinburgh (prior to 1927) very common
Splenomegaly	Less than 10%	Edinburgh (prior to 1927) 33%
Weakness and tiredness	100%	==
Dyspnœa on effort	80%	==
Vague dyspepsia	50%	==
Pallor of mucous membranes	100%	==

oral liver therapy. Although the reticulocyte had been described for many years before the discovery of liver therapy, the reticulocyte count only received general acceptance as a valuable test for the assessment of therapeutic agents in hæmatology subsequent to the appearance in 1926 of Minot and Murphy's report on the treatment of pernicious anæmia with liver.

PERIOD 2, ABERDEEN, 1930-38

On arrival in Aberdeen in 1930, I found that the Department of Medicine consisted solely of a lecture room and a retiring room and that the staff allocated to the Professor consisted of one part-time Assistant. My request to the University authorities for laboratory accommodation was granted and temporary buildings were rapidly erected, while preparations were made for the erection of a new hospital and medical school. A great deal of my time was devoted

to these developments, but unfortunately I had the pleasure of working for less than two years in these splendid new buildings before I was recalled to Edinburgh in 1938. During my period of office in Aberdeen I was very fortunate in my selection of staff for the Department of Medicine. The first Assistant whom I chose was Dr McMichael, now Professor of Medicine in the Post-graduate Hospital, Hammer-smith, London, the second was Dr Hill, now Professor of Medicine in Dundee, and my third was Dr Fullerton, who is the present occupant of the Chair of Medicine in Aberdeen.

Of the many hæmatological experiences in Aberdeen, three stand out prominently in my memory despite the lapse of time. The first was an attempt to produce an extract from fish livers on a large scale. I had high hopes not only for the therapeutic value of such an extract in pernicious anæmia, but also for its commercial value as a new enterprise which might help the fishing industry which was in a state of grave depression and unemployment at that time. The first step was to obtain the help of an industrial chemist to solve the problem of how to extract the oil from fish liver without damaging the oil or the residue from which would be secured the anti-pernicious anæmia principle. The second step was to establish a satisfactory method of extracting the anti-anæmic principle from the fish residues in a potent and palatable form. The third step was to prove the potency of the liver extract by clinical trials on patients, and the last step, if the first three were successful, was to persuade an industrialist to set up a large-scale manufacturing plant. Complete success attended the first three steps of this enterprise, a palatable product was produced from fish livers which induced excellent clinical and hæmatological results in patients with pernicious anæmia in a dose as low as a teaspoonful thrice daily (Davidson, 1932). It is therefore sad to relate that all these efforts came to nothing and the enterprise had to be abandoned because it became apparent just when commercial production of fish liver extract was about to start that oral liver therapy would be permanently supplanted by parenteral liver therapy which had been shown to be so much more effective.

The second experience to which I should like to refer is connected with the interesting problem of the megaloblastic anæmias refractory to the parenteral injection of potent refined liver extracts. My investigations into this problem, which have been proceeding for nearly twenty years, originated in Aberdeen as a result of certain observations which I made on a case of megaloblastic anæmia associated with the tropical sprue syndrome. The patient had a fatty diarrhœa and had lost six stones of weight within the twelve months prior to admission to my unit. The blood count was under one million red cells and the blood picture was typical of pernicious anæmia. The patient failed to respond to the injection of ample amounts of Campolon and Anahæmin and would undoubtedly have died if I had not put him on to a high protein diet containing half a pound of liver daily by mouth.

A remarkable hæmatological and clinical remission resulted, including the return of free hydrochloric acid to the gastric juice. On the basis of these observations, I suggested nearly twenty years ago that the chemical fractionisation of liver extracts for parenteral use removed some essential factor which was necessary for the restoration of normal blood formation in certain types of megaloblastic anæmia. Many years were to elapse before the discovery of folic acid was made. This claim has been confirmed in many parts of the world and has been shown to be equally applicable to vitamin B₁₂ which is also an ineffective therapeutic agent in certain types of megaloblastic anæmia. A series of reports have been published from my department during the past twenty years dealing with various aspects of the refractory megaloblastic anæmias associated with pregnancy, malnutrition, malabsorption and from no known cause.

The third and last impression I have of my work in Aberdeen is connected with a group of anæmias due to iron deficiency. Unemployment was rife in the city and large numbers of women were referred to our Blood Clinics with hypochromic anæmia of great severity. It soon became apparent to me that however intriguing and exciting were the megaloblastic anæmias, their rarity compared to the iron deficiency anæmias made them of little economical or sociological importance in this community. It was the realisation of this point that induced Fullerton and myself to undertake a large-scale assessment of the hæmoglobin levels of an unselected section of the community comprising individuals of both sexes and all ages from infancy to old age. Nearly 3000 unselected individuals had their hæmoglobin levels estimated and the results were published with an accompanying graph (Davidson, Fullerton and Campbell, 1935). It is my belief that this paper and its graph fulfilled a useful purpose in bringing the attention of the medical profession not only in Great Britain but in other parts of the world to the great frequency of iron deficiency anæmia, its sociological and economic implications and to the vulnerability of certain groups to this form of anæmia, namely infants and women of the child-bearing age.

PERIOD 3, EDINBURGH, 1939-51

One of the most interesting medical changes which has occurred in Edinburgh during the past twenty-five years is the great expansion and improvement of the facilities for the investigation and treatment of diseases of the blood available to the doctors and their patients in the South-East region of Scotland. Up to the time of the retiral of Professor Gulland in 1928, his staff consisted of one part-time assistant paid by the University, and one part-time Clinical Tutor paid by the Royal Infirmary. There was no laboratory accommodation available to him and his staff either in the Department of Medicine or in the Royal Infirmary. When his successor, Professor W. T. Ritchie, retired in

1938 the Department of Medicine in the University contained five rooms, fitted up as laboratories and offices, and a large demonstration room for teaching purposes, while the staff consisted of one full-time Lecturer and two Assistants. At the present time the accommodation of the University Department of Medicine is more than double that available to my predecessor, while my staff includes 7 full-time Lecturers, 4 part-time Lecturers, 4 full-time Assistants in addition to a large number of Registrars and Senior House Officers working in the Professorial Medical Units located in various hospitals in Edinburgh. The need for a great increase in staff was accepted by the University Court when it approved of my policy of developing special units for teaching and research in hæmatology, rheumatology, gastro-enterology, cardiology, neurology, nutrition and diseases of the respiratory tract. In the division of hæmatology, I have a medical staff of one full-time and two part-time Lecturers, two Assistants, and one hæmatological Registrar, while the non-medical staff consists of four technicians trained in hæmatological methods. In addition to accommodation located in the University and in the Clinical Research Laboratory in the Royal Infirmary, the Board of Management of the hospital has provided me with consulting rooms, waiting rooms, offices for secretaries and for filing records, and hæmatological laboratories for servicing the special clinics for the investigation and treatment of diseases of the blood. It would indeed be extraordinary, therefore, if the services available in Edinburgh at the present time were not incomparably superior both in quantity and quality to those in operation twenty-five years ago, when a part-time Professor of Medicine, who was fully occupied by a vast consulting practice, was provided with one part-time Assistant and no laboratory accommodation in hospital.

Many thousands of patients suffering from all kinds of blood disorders have been referred to my unit for a hæmatological opinion during the past eleven years. A survey of this mass of clinical material makes it clear that the megaloblastic anæmias comprise a relatively rare group of blood diseases. During this period (1940-51) we have seen 713 cases of macrocytic anæmia as judged by the colour index and mean cell volume being above the upper limits of normal. Table II shows that 577 of these cases were proved to be associated with a megaloblastic marrow. While it is obvious that all macrocytic anæmias are not necessarily megaloblastic, it is true to say that in Scotland the chance appears to be about 5/1 that macrocytosis of the circulating erythrocytes will be associated with megaloblastosis of the bone marrow. Table I also clearly shows that Addisonian pernicious anæmia is by far the commonest type of megaloblastic anæmia in Scotland.

The Megaloblastic Anæmia of Pregnancy—Sufficient time remains for me to deal only with one group of the megaloblastic anæmias, namely that associated with pregnancy and the puerperium. During the past eleven years, we have studied 42 cases belonging to this group. The rarity of this form of anæmia is emphasised by the fact that we

encounter in Edinburgh only one case of the megaloblastic anæmia of pregnancy for every 18 cases of Addisonian pernicious anæmia, which in itself is an uncommon disease. Dr Clark, one of my Lecturers in hæmatology, has recently made a careful study of 18 cases of megaloblastic

TABLE II

Macrocytic Anæmias 1940-51

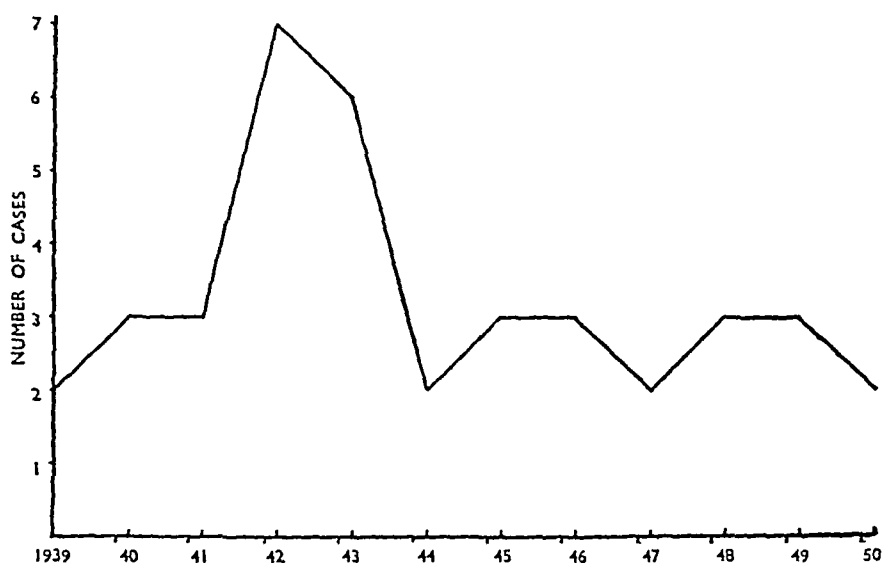
Diagnosis —	
Addisonian pernicious anæmia	489
Mal-absorption syndrome	61
Megaloblastic anæmia of pregnancy	42
Idiopathic refractory megaloblastic anæmia	14
Hypoplastic anæmia and aplastic anæmia	25
Hæmolytic anæmia	21
Miscellaneous, including diseases of the liver	61
<hr/>	
Total number of cases of macrocytic anæmia	<u>713</u>
Of these, the following have been found to have a megaloblastic marrow —	
1 Addisonian pernicious anæmia	489
2 Megaloblastic anæmia of pregnancy	42
3 Megaloblastic anæmia of the mal-absorption syndrome	
(a) Tropical sprue	30
(b) Idiopathic steatorrhœa	
(c) Post-gastrectomy (one case)	
4 Idiopathic refractory megaloblastic anæmia (refractory to parenteral liver therapy for no ascertainable cause)	14
5 Megaloblastic anæmia of liver disease	2
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Total number of cases of megaloblastic anæmia	<u>577</u>
<hr/>	
Total number of cases of macrocytic anæmia with normoblastic marrow	<u>136</u>

blastic anæmia, investigated in my unit during the past seven years, with the object of seeing whether they differ in any material respect from some 16 cases which we reported in the *British Medical Journal* ten years ago (Davidson, Davis and Innes, 1942). The result of this investigation will be appearing in the near future in the *Edinburgh Medical Journal*. The principal features previously noted by us have been again confirmed, namely —

- (1) the need for examination of the bone marrow for diagnostic purposes, because of the frequency with which the colour index and mean cell volume may be within or even below the values accepted as normal,
- (2) the frequency with which free hydrochloric acid is found in the gastric juice, and
- (3) the refractoriness of this group of megaloblastic anæmias to the parenteral injection of liver extract or vitamin B₁₂, and their immediate response to the oral ingestion of proteolysed liver or folic acid

Dr Clark has also estimated the ratio of cases of megaloblastic anæmia of pregnancy developing in women admitted to the Simpson Maternity Hospital, Edinburgh, over a period of seven years in relation to the number of deliveries over the same period. He concludes that the disease occurs in about one in every two thousand pregnant women admitted to this Maternity Hospital. He also draws attention to the rarity of the disease as indicated by the fact that out of the many hundreds of cases of anæmia investigated in the Blood Clinic in Edinburgh every year, only two or three belong to this group. I have constructed a graph (see Graph 1), to indicate not only the rarity

Annual Incidence of Megaloblastic Anæmias of Pregnancy and the Puerperium in Edinburgh 1939-50



GRAPH 1

of the disease, as judged by its average annual incidence during the past seven years, but also the remarkable fact that during the period 1941-43 the incidence of the disease in Edinburgh appears to be two or three times as great as in recent years. Is this finding to be dismissed as being purely fortuitous or is to be attributed to the fact that during these years Britain's war-time diet was at its lowest nutritional level in many respects and especially in animal protein? From 1943 onwards, when the submarine danger was being gradually controlled, not only were Britain's nutritional requirements more adequately satisfied by imports from overseas but the general standard of nutrition of the poorer sections of the nation, who prior to the war existed in the shadow of unemployment or partial employment, markedly improved consequent on full employment, higher wages and a more equal distribution of nutrients through the channels of rationing, school meals and special social services.

mild degree of hæmolytic anæmia. Subsequent to delivery she continued to suffer from acholuric jaundice, and accordingly some months later she was treated with ACTH without any effect on the hæmolytic process, and later by splenectomy with entirely successful results. It is reasonable to suppose that the additional strain of pregnancy lead to the development of a megaloblastic anæmia by increasing the needs for hæmopoietic factors in a patient whose requirements were already greater than normal because of pre-existing hæmolytic anæmia.

In conclusion, I would like to express my gratitude to Providence for the fortunate chance which lead me as a young man into the fields of hæmatology, as in my opinion no branch of medicine during the past thirty years has offered greater or more exciting opportunities to the clinician and the research worker.

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DERMATOMYOSITIS A CASE REPORT

By H G HOWELL RICHARDS, M B, Ch B, M R C P E

Department of Pathology, Royal Hants County Hospital, Winchester

DERMATOMYOSITIS is a non-suppurative inflammation of skeletal muscle, skin, sometimes the myocardium, and occasionally accompanied by lesions of the alimentary tract. Diagnosis in life is often difficult, for which reason, together with its comparative rarity, the case about to be described is thought worthy of publication.

The ætiology is still obscure and many authors regard it as directly or indirectly of infective origin. O'Leary, Warsam, and Morris believe that antecedent acute infections, focal sepsis, pulmonary disease or parturition play a prominent part. For 5 out of 40 cases they claimed to isolate streptococci, which, when injected into animals, produced hæmorrhagic lesions of skin and muscle. Lamb described a case in which complement fixation tests against streptococci were positive, and the patient's blood agglutinated autogenous streptococci from the nasopharynx. Holmes recorded the recovery of streptoviridans from the muscle of a histologically proven case, although he was unable to culture an organism from the blood.

Nevertheless, in spite of these facts the role of bacteria in this disease appears as problematical as in rheumatoid arthritis and the so-called "collagen diseases."

The age period at which the disease occurs varies from childhood to old age with a maximum incidence at the fifth decade, but the incidence is roughly equal in the two sexes.

Clinically, the diagnosis may be extremely difficult because of the various modes of onset. In some the dermal lesions appear first, in others the muscular, or both components may appear together. Finally, vasomotor symptoms of the Raynaud type, or simulating vascular thromboses may open the story. In Lewis' case thromboses were ultimately demonstrated.

The dermal manifestation may start as a diffuse erythema similar in appearance and distribution to lupus erythematosus, or as in the author's case, it may resemble pityriasis rubra. In the case described by Holmes a musculo-erythematous rash with petechial hæmorrhages developed over the limbs, Goldman's patient suffered a vesiculated keratotic eruption of the extremities. Œdema usually accompanies the florid exanthemata, and with the passage of time the lesion becomes widespread and sclerodermatous.

The muscular symptoms may affect any part, but predominantly the shoulder girdle, arms and neck. Eventually the entire voluntary muscular system may appear involved—pain, progressive wasting, and

profound weakness The downhill course is generally relentless until death due to respiratory or pharyngeal myopathy terminates the issue The rate of progress is very variable, however, the patient may be dead in a few months, or, waxing and waning, linger on for five or six years

The morbid anatomical and histological features are well exemplified by the following case in which, however, the dermal lesions preceded the muscular, and never reached the sclerodermal stage

CLINICAL HISTORY

Mr A K, aged 36 at time of death

In November 1948 a skin eruption commenced over the hands and feet In February 1949 Dr A S Hall saw the patient for the first time, and noted a diffuse erythema of the hands and feet, wrists, forearms, shins, knees, groins and genitalia, with considerable thickening and scaling Marked fissuring at the joint folds limited movements

The scalp was also covered with scales and thickened, although there was no loss of hair The angles of the mouth were fissured and the buccal mucosa reddened, thickened and denuded

Generalised lymphadenopathy and œdema of the ankles was present, but without visceral enlargement No abnormality of muscle power, the blood picture, urine, or radiological appearance of the chest A diagnosis of Pityriasis Rubra was made

Shortly after this time "pins and needles" developed in the forearms, together with numbness in the middle fingers of each hand

By June 1949 symptomatic treatment had greatly improved the skin lesions although erythema remained, increasing muscular weakness with wasting (upper limbs), kyphosis, dysphagia and dyspnoea now became evident, and a diagnosis of dermatomyositis was now considered by Dr Hall and Dr

M Robertson A month later, due to weakness of the neck muscles, the patient was unable to hold his head up, and complained of a sense of dull pressure about the neck and left shoulder The muscular symptoms tended to be relieved by rest He had lost about two stone since leaving the army, but his appetite and digestion were normal Nothing relevant in his past history

On 3 8 49 it was noticed that the hands, feet, and nails showed marked parakeratosis, but diffuse erythema with desquamation was present on the distal halves of all four limbs

By September 1949 his condition had deteriorated and on examination showed —

CNS—Cranial nerves —Normal apart from doubtful weakness of the right facial muscles, wasting of the trapezius muscles and tongue

Upper and lower limbs —Marked muscular wasting and weakness, maximal proximally, and symmetrical, tendon reflexes normal apart from absence of knee jerks

Abdominal and plantar reflexes —Normal

No abnormalities of the sensory system, no tremors or muscular fibrillation

Marked wasting of neck and shoulder muscles, especially trapezi, scapular and posterior cervical

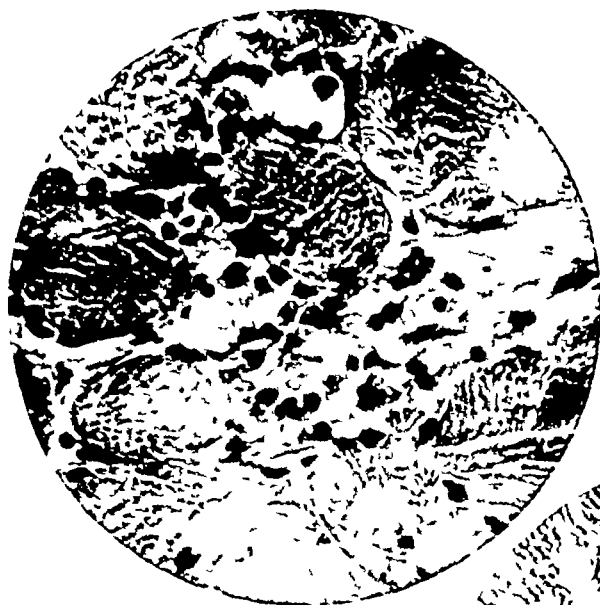
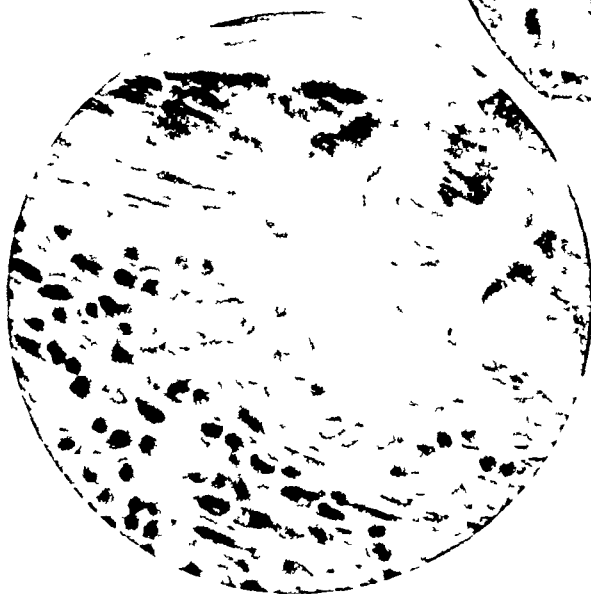


FIG 1 —Biopsy one month before death
Noted isolated interstitial lesion High
power view

FIG 2 —Biopsy one month before death
Note solitary hyaline muscle fibre in
centre High power view



FIG 3 —Section taken at autopsy Inter
stitial infiltration by round cells High
power view



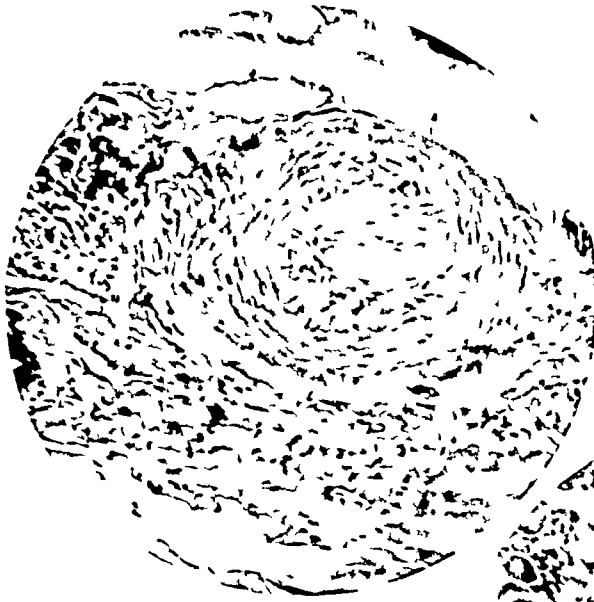


FIG 5—Section taken at autopsy. Skeletal muscle showing marked discrepancy in size of muscle fibres. Low power view.

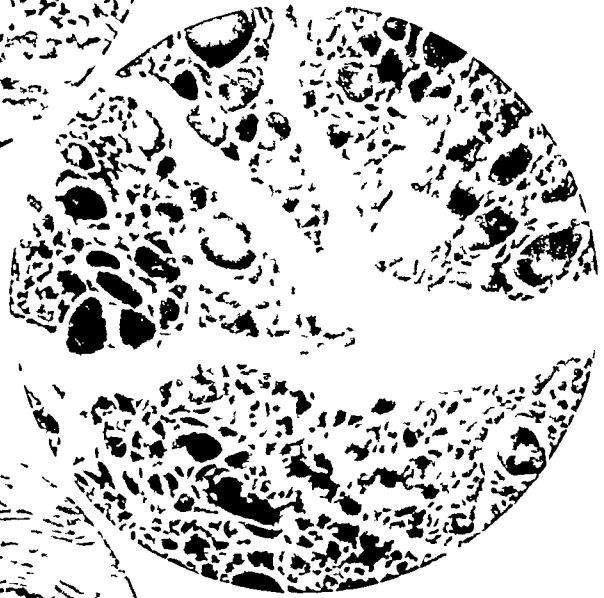


FIG 4—Section taken at autopsy. Vascular lesion showing marked endarteritis. Low power view.

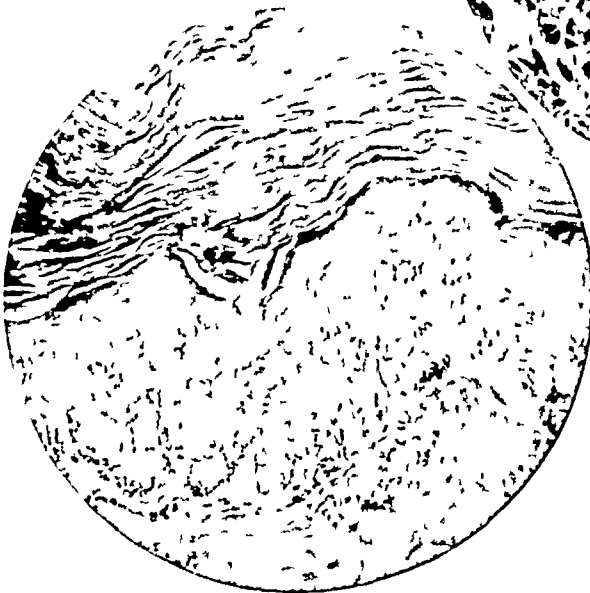


FIG 6—Section taken at autopsy. Note hyperkeratosis and diffuse round cell infiltration of corium. Low power view.

Cardiovascular and respiratory systems, and abdomen —Normal
Temperature —Normal

Investigations

Blood Counts —Hb varied between 78 and 90 per cent White cell counts —

17.2.49 Wbc 10,400 per c mm (polymorphs 76 per cent, lymphocytes 16 per cent, monocytes 4 per cent, eosinophils 2 per cent)

27.5.49 Wbc 8000 per c mm (polymorphs 75 per cent, lymphocytes 19 per cent, monocytes 3 per cent, eosinophils 3 per cent)

29.7.49 Wbc 7600 per c mm (polymorphs 66 per cent, lymphocytes 22 per cent, monocytes 5 per cent, eosinophils 6 per cent, basophils 1 per cent)

C S F —29.7.49 Chlorides 740 mgms per cent Protein 25 mgms per cent Sugar 65 mgms per cent No cells seen W R negative Lange normal

Surgical Biopsy (29.7.49) —Section of left pectoralis major —“ In the main the muscle fibres appear normal but interstitial collections of round cells (mostly lymphocytes), together with scanty and pyknotic polymorphs form fairly numerous foci. Where these occur the muscle fibres appear a little more hyaline than elsewhere. Although the round cell foci are usually associated with dilated capillaries there is nothing resembling actual arteritis. In places the foci appear associated with nerve tissue although not all nerve elements are affected.

The possibilities in my opinion are —

- 1 Polyneuritis
- 2 Myasthenia gravis
- 2 Polyarteritis (A typical lesion not having occurred in this section)

Muscle Intensity Duration Curves (3.8.49) —

Normal graphs, i.e. normal conductivity in nerves and normal excitability of muscles

X-rays —Chest, skull, cervical and dorsal spine —normal

On 31st August the patient was seen by Dr J. St C. Elkington at St Thomas's Hospital, he suggested a possible diagnosis of dermatomyositis in which the original skin lesion was settling with very little chronic sclerodermatous change. The patient was returned to Winchester, where early in September he was temporarily discharged to his home to settle personal affairs. While there he died suddenly.

AUTOPSY REPORT (29.9.49)

Short stature, narrow build wasting of skeletal muscles generally, but maximally in shoulder girdles, upper limbs, and thoracic muscles. Marked thickening of all digital nails.

Marked hyperkeratinisation of soles of feet and both hypothenar eminences. No identifiable cutaneous eruption.

Dissection of skeletal muscles —Marked pallor of those about the thorax and upper limbs, except where post-mortem lividity is evident over the dorsum.

Serosæ

Peritoneum and pericardium —Normal Pleuræ, normal apart from a few adhesions on left side along anterior border of upper lobe

Tongue —Lymphoid tissue at its root is unduly prominent

Pharynx and Larynx —Normal

Trachea and Main Bronchi —Contain abundant muco-pus, bronchi appear congested

Thyroid —Normal

Mediastinal Lymph Nodes —Paratracheal, tracheo-bronchial and broncho-pulmonary on both sides appear a little enlarged, congested and œdematous

Lungs —No acute pleurisy Both organs appear congested, œdematous, and show extensive broncho-pneumonia mainly in lower lobes

Heart —300 gm in weight

Pericardium —Normal The myocardium, valve cusps, endocardium and coronary arteries are normal

Aorta and Pulmonary Artery —Normal including valve cusps

Celiac Axis, Splenic Artery, etc —Normal

Adrenals, pancreas, œsophagus, stomach, duodenum, small and large

Intestine —Normal

Spleen —260 gm Nearly twice normal size, normal shape Section, malpighian bodies appear extremely numerous and a little enlarged, they almost resemble those in "sago" spleen

Liver —2371 gm Enlarged Normal shape Section, general appearance of cloudy swelling

Urinary Tract —Normal apart from vascular congestion of the kidneys

Prostate and Rectum —Normal

Superficial and Abdominal Lymph Nodes —Normal

Brain —Externally and on section it appears normal

Histology

Skeletal Muscles —Sections taken from the pectoral, dorsal, trapezius and psoas muscles are extremely striking The changes observed are advanced but may be divided into those of (a) muscle fibres, (b) interstitial tissue, (c) arteries

The majority of muscle fibres are affected to a greater or lesser degree, initially they show an apparent increase in sarco-lemmal nuclei, together with separation of the myofibrils Here and there a muscle loses its transverse striations and becomes completely hyaline, while in transverse section some exhibit a central vacuole In more severely affected parts the muscle fibres undergo longitudinal splitting, become zig-zag in shape, and finally are broken into small fragments which tend to take on a bluish colour with hæmatoxylin-eosin, they are obviously being phagocytosed by mobile cells of the interstitium In some parts of a particular section myolysis is less evident, but the muscle fibres become completely hyaline and converted to collagen Muscle fibres of widely varying sizes may be seen in the same low power field

The interstitial changes are very variable, in places there is intense cellular infiltration by mobile elements, predominantly mononuclear—lymphocytes, plasma cells, elongated or polygonal sarcoblasts In other parts the interstitium is only moderately cellular but appears swollen and œdematous, so

that muscle fibres are widely spaced apart. Finally, in the most advanced lesions fibrosis obliterates both cellular interstitial tissue and muscle fibres.

The vascular lesions are those of endarteritis medial and intimal thickening (the latter in part may be due to oedema). The vessels involved are the small arteries and arterioles, but the interstitial inflammation is not obviously perivascular, and there is minimal evidence of invasion of the vessels by mobile cells, or their implication by necrosis of the polyarteritis nodosa type.

Skin—Sections from the plantar surface of the foot and palm of the hand show marked hyperkeratosis, diffuse low grade round cell infiltration in the subepithelial papillae, together with a few perivascular round cell infiltrations in the deeper corium, medial and intimal thickening is seen in some small arteries. Here and there fragments of underlying striated muscle show marked hyaline change, but without pronounced cellular reaction around them.

The skin over the scapula exhibited more definite abnormality—the epithelium is thin but the underlying corium is dense and contains fairly numerous "lymphorrhages," i.e., perivascular round cell collections. Arterial changes as above are also present.

Tongue—Fairly severe myositis together with round cell infiltration of the corium. The squamous epithelium shows excessive "scaling" and appears acanthotic.

Larynx—Shows a diffuse round cell infiltration beneath the epithelium, and a low grade myositis.

Heart—Sections from right and left ventricles appear normal.

Lung—Acute broncho pneumonia.

Spleen—Shows changes characteristic of septic spleen.

Liver, Kidney, Adrenal and Brain—Congestion and post-mortem autolysis.

Avillary and Lumbar Plexuses—No evidence of neuritis, but obvious myositis is present in adjacent skeletal muscle.

DISCUSSION

This case was submitted to Dr W. Freudenthal, who very kindly gave his opinion that the histological lesions are indistinguishable in the muscles from those in dermatomyositis, those in the skin although slight are nevertheless suggestive.

A study of the literature shows that dermatomyositis not infrequently presents initially as a cutaneous disease. O'Leary *et al.*, reviewing 40 cases, found that in 14 oedema and cutaneous lesions ushered in the illness, while Goldman described a proven case in a man of 63 which started with a vesicular and keratotic eruption of hands and toes, muscular weakness was not manifest for fifteen months but then came on suddenly, developed extensively and terminated in death less than two months later. The author's case, it will be remembered, showed minimal lesions in the muscle biopsy less than a month before death, yet at autopsy every single portion of skeletal muscle sectioned showed clearly demonstrable changes.

Reviewing the muscle biopsy (taken one month before death)

in retrospect it is evident that unless one is familiar with the condition there is little on which to base a correct diagnosis

However, on comparing it with a section of normal pectoral muscle it becomes apparent that certain features had either been overlooked or wrongly interpreted, *z e*

(1) Sarcolemmal nuclei appear on the whole more numerous and larger than normal

(2) Occasional muscle fibres show pale, central hyaline zones quite unlike anything seen in the normal Such fibres are often isolated, and not necessarily associated interstitial lesions

(3) The interstitial collections of mobile cells, though small, are characteristic of myositis although at this stage the adjacent muscle fibres are often showing little or no change Elements at first mistaken for nerve cells are, in point of fact, sarcoblasts

Comparing the muscle biopsy obtained during life with sections from the same removed at autopsy it thus becomes apparent that within the space of about one month a remarkable advance had taken place in the disease—if we assume that the biopsy fragment was representative of the skeletal tissue as a whole Further, it demonstrates that clinical signs may be well established when histological abnormality is relatively slight, this may account for Foots' observation that "this is becoming the bane of the surgical pathologist, as its presence is often suspected by the clinician, and its lesions are not often demonstrable in the muscle and skin sent in for pathological examination"

The surgical pathologist examining a muscle biopsy may have to distinguish this disease from certain other possibilities —(1) Weil's disease, (2) acute myositis, (3) myasthenia gravis, (4) trichiniasis, (5) polyarteritis nodosa

In the majority of cases his task will be easy if he has access to clinical details, and if he bears the following points in mind —In Weil's disease the muscular lesion is one of patchy hyaline degeneration, with a striking vacuolation of the muscle fibres, there is negligible interstitial infiltration by mobile cells (in contrast to dermatomyositis) but swelling and proliferation of sarcolemmal nuclei is an important feature

In acute myositis suppurative lesions of various sizes occasionally complicate typhoid fever or pyogenic infections, but their acute nature as well as the clinical circumstances usually facilitate diagnosis A variation on this theme is found in the focal hæmorrhagic muscular necrosis sometimes seen in acute infections, and which, when accompanied by extensive hyaline change in the fibres, is known as Zenker's degeneration, while the appearances of individual muscle fibres may resemble dermatomyositis the interstitial lesions are mainly œdema, fibrin deposition and hæmorrhage

Trichiniasis — The interstitial reaction again may resemble dermatomyositis, but the presence of larvæ and focal necrosis is distinctive Likewise, in polyarteritis nodosa the fibrinoid vascular lesions and necroses are characteristic and diagnostic

SUMMARY

(1) A case of dermatomyositis, in which the cutaneous manifestations preceded the muscular by several months, is described

(2) The autopsy findings are reported, and the histological features compared with a biopsy of muscle taken during life, marked differences in degree are noted and discussed with a view to future diagnosis during life by means of biopsy examination

The author is greatly indebted to Drs A S Hall and K M Robertson for access to the clinical data of this case

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RETINAL CHANGES IN HYPERTENSION

By JOHN MACASKILL, M B, F R C S E, D O M S

THE changes sometimes seen in the fundus of the eye in association with raised blood pressure have attracted attention almost since the time when this region could be observed. For here, as in no place else in the body, it is possible, in life, to view the finer branches of the great vascular tree and to observe any changes in the tissue they serve.

The introduction of the ophthalmoscope added greatly to the knowledge of those changes and resulted in the accumulation of a large literature on them. It is appropriate, therefore, this year to pay tribute to Helmholtz, who first introduced his ophthalmoscope exactly one hundred years ago. Inevitably, the changes which we now associate with raised arterial tension attracted notice and in 1876 Gowers remarked on the changes in the retinal arteries in certain patients with chronic Bright's disease in whom the blood pressure was raised. A few years later Gunn gave the first detailed description of those changes and all subsequent writers have recognised the accuracy of his descriptions. He realised that the changes in the retinal vessels were related to hypertension and noted that they may be present when there was no evidence of kidney disease. Early in this century Foster Moore elaborated, and added to, Gunn's description and correlated the retinal changes with those found elsewhere in the body. He showed the relation of "arterio-sclerotic retinitis" to vascular sclerosis and distinguished the condition from these changes in the retina now recognised as the retinopathy of malignant hypertension. The changes in this latter condition and their significance has formed the studies of many subsequent writers, notably Volhard, Keith and Wagener, and Fishberg.

ASPECTS OF THE NORMAL FUNDUS — Before passing to a consideration of abnormal changes, it is perhaps well to consider some aspects of the normal fundus. One is apt to forget, when using the electric ophthalmoscope, that a very magnified image is obtained, one of sixteen diametres in fact, and if it is remembered that the optic disc is only 1.5 mm in diameter, then the minute and often microscopic nature of many of the changes seen will be realised. In this respect, too, the minute calibre of even the bigger vessels will be appreciated, something of the order of 0.25 mm or less, and there has been controversy whether they are not rightly regarded as arterioles. Maximow and Bloom classify as arterioles those branches of the arterial system with a diameter of 0.3 mm or less, so that if this is accepted then the retinal vessels can be so regarded.

The walls of the retinal vessels are very poorly developed and this renders them translucent, so that what is viewed as a retinal artery is indeed the blood column contained within this translucent tube.

A Honyman Gillespie Lecture given 14th June 1951

CHANGES IN THE RETINAL VESSELS WITH AGE —Gowers stated, that in a retina free from local disease any marked change in the vessels might be taken as evidence of a similar change elsewhere in the body, and it is well to have in mind that sclerotic vascular changes, of which the most common cause is hypertension, occur also in other conditions such as diabetes and syphilis. The changes in the retinal vessels which are said to accompany old age warrant some attention, for raised blood pressure frequently occurs in the later decades of life when the ageing process is giving rise to changes elsewhere in the body.

It is within the experience of all who have the opportunity of examining many fundi that many old, sometimes very old people, have perfectly normal retinal blood vessels when viewed by the ophthalmoscope. Their appearance and calibre and the arterio-venous crossings are absolutely normal. Gunn, writing on the retinal vascular sclerosis which he was observing stated, "that such changes do not occur from age alone" and added that many old persons of seventy to eighty years of age have perfectly normal blood vessels. Fishberg in studies with Oppenheimer found, in old individuals with extreme arterio-sclerosis of the palpable vessels but with no evidence of present or antecedent hypertension, that sclerosis of the retinal vessels was absent or minimal, while Foster Moore found normal retinal vessels in life in cases in whom, at post mortem, gross atheromatous changes of the big vessels were seen, in those cases in whom there had been no rise in blood pressure. Numerous other writers have come to similar conclusions, but Pines and Duke-Elder are not so absolute in their statements and believe some slight changes in the retinal vessels do occur from age alone, but that they are "not markedly visible in the absence of hypertension."

It is difficult to believe that the retinal vessels would be immune from the changes which occur everywhere in the body from age. Ballantyne, Michaelson and Heggie showed that changes in the intima could take place without any apparent change in the vessel wall seen ophthalmoscopically, the translucency was not interfered with although some alteration in the blood column was seen where the intimal changes were marked. Similarly, Bridgett in 17 cases with ophthalmoscopically normal vessels found that in only 7 cases were the vessels also histologically normal.

CLASSIFICATION OF THE RETINAL CHANGES IN HYPERTENSION — I have reviewed a series of unselected cases showing hypertensive changes which were seen in the eye department. In some the changes were seen in the course of routine examination, in others some happening had given rise to alteration of vision which had caused the patient to seek advice, and a few were known cases of hypertension sent for opinion on the fundi. All were examined in the dark room, some on several occasions over a period of some months. I am indebted to Dr Trevor Kinnear for much help from the general medical aspect of the cases, and it is a pleasure to record my thanks to him. The blood pressure was recorded in all in some a re as availab

after rest in bed for some days, but in the majority the readings are those taken in the out-patient department and on this account may be somewhat high, but as this possible error is common to all groups it hardly affects comparison between them. Only cases in whom positive fundus changes were present in association with hypertension are included, so it may not be out of place to mention the many cases of low grades of arterial hypertension in which there are no changes in the retinal vessels or in the retina.

Although in past years much has been learned of the clinical pattern of hypertension, the causative factors remain unknown, in consequence, classification presents a difficulty and the varied terminology which has been used gives expression to this. Volhard and Fahr realised that one group, with distinctive features in the retinal vessels, followed a relatively benign course, and was compatible with fair health and moderate length of years. Another group, which they called malignant hypertension, also had characteristic retinal features but ran a short and severe course ending in early death. Keith, Wagener and Barker enlarged on this classification, sub-dividing each group into two to make four groups, and as the vascular changes were essentially arteriolar, they used the general term of diffuse arteriolar disease with hypertension.

MODERATE ARTERIOLAR SCLEROSIS WITH HYPERTENSION —Keith, Wagener and Barker's first group is that in which there is only vascular sclerosis present with a mild degree of hypertension. This shows itself by an increase in the brightness of the arterial reflex which imparts to it a burnished appearance which has been found to correspond with thickening of the media. In estimating this change it must be remembered that an exaggeration of the normal reflex is being observed, and on this account the interpretation of this sign is capable of wide error. For such an observation to have any value the "copper wire" appearance of the retinal vessels must be quite marked and distinct. Keith, Wagener and Barker found the average age of hypertensives showing this early vascular sclerosis to be fifty-five. The hypertension, they noted, can be of long duration without impairing general health, does not rise to extreme heights and is the commonest variety met with in practice. I cannot speak of the length of life of the individuals in the group, but they were mainly noted in routine examination and were apparently not complaining of any great disturbance in health. It is noteworthy, too, that in this group no retinal changes, or ocular complications of hypertension, were present.

MARKED RETINAL ARTERIOLAR SCLEROSIS WITH HYPERTENSION —With raised blood pressure of a higher order the vascular sclerosis becomes more marked and additional changes may be seen. Keith, Wagener and Barker classed such cases as Group II, and this group, they noted, was associated with a higher and more sustained hypertension, a moderate degree of wellbeing in many cases, and certain patients belonging to this group, they found, lived comfortably for many years.

Changes at Arterio-venous Crossings —The increase in the sclerosis of the media shows itself by reduction in the translucency of the arterial wall, so that if the point where an artery crosses a vein is observed, not only is the vein concealed, but it appears to be separated from the artery by a small interval which corresponds to the sclerosed arterial wall seen end on

Sallmann has shown, by histological examination, that a corresponding increase in the connective tissue of the adventitia takes place, and that the artery and vein have a continuous meshwork of adventitia enfolding them at the arteriovenous crossings. Increase of the adventitia in this region results in the vein becoming partially obscured near the artery, and gives the impression of it tapering on either side of it

Gunn saw in many cases of vascular sclerosis with marked hypertension other changes at the arterio-venous crossings. In some, the vein on the peripheral side of an arterio-venous crossings appeared to dilate as if to form a little ampulla. Gunn thought—and most people accept the view—that this resulted from mechanical obstruction to the venous backflow, but against this simple explanation is the occurrence in some cases of a similar dilatation of the vein on the other side of the crossing. Whatever is the pathology giving rise to the change, there is no doubt, as Gunn pointed out, that it occurs in association with marked vascular sclerosis and considerable hypertension and is, of course, well known as Gunn's sign

Normally when a vein crosses obliquely beneath an artery the line of direction of the vein is unaltered. Foster Moore drew attention to an alteration in this state in certain cases wherein a well developed degree of vascular sclerosis and hypertension was present. The vein at the crossing appears to change direction and crosses the artery approximately at right angles, thereafter continuing its course. It might be thought that this was merely displacement by a thickened arterial wall, but a precisely similar effect has been seen when the vein crosses superficial to the artery

All studies of the retinal changes in hypertension have shown that the changes described at the arterio-venous crossings occur in the presence of well-developed vascular sclerosis and hypertension. In contrast to the change in appearance of the vessel wall which is capable of wide individual interpretation, the changes at the arterio-venous crossings are definite and positive and so form a most useful sign in the retina of vascular sclerosis and of the presence of hypertension

To underline the importance of the changes at the arterio-venous crossings I have divided up those cases which would fall into Keith, Wagener and Barker's Group II, into those with slight changes at the arterio-venous crossings and those in whom those changes were severe (Table I). It will be seen that the hypertension is markedly higher in the second group and in this group too, secondary retinal changes make their appearance and the incidence of complications becomes greater

Changes in Calibre—Apart from the periodic spasm which may occur in vessels in this group of hypertension and which will be referred to later, there is evidence that a generalised reduction in calibre due to increased tone may be present. This is a very difficult observation

TABLE I

	Age		Blood Pressure			Retinal Changes	Complications	Cases
	Range	Mean	Syst	Dias	Mean			
Vascular sclerosis only	43-76	58	130-210	80-130	$\frac{161}{92}$	None	None	8
Vascular sclerosis with slight "A V" changes	38-70	60	130-230	82-130	$\frac{179}{102}$	None	Venous thrombosis 2 Vaso spasm 1	7 7
Vascular sclerosis with marked "A V" changes	47-78	63	170-260	100-155	$\frac{215}{122}$	Hæmorrhages 5 'Arterio-sclerotic retinitis' 4	Arterial occlusion 4 Venous thrombosis 3 Vaso spasm 1 Optic atrophy 1	18
Acute angiospastic retinopathy	34-54	46	220-260	130-140	$\frac{247}{135}$	Retinopathy	"Amaurosis fugax"	1 3

to make unless it is extreme and requires repeated examination to be certain of its presence—for it is to be remembered that a very wide variation may be seen in the calibre of normal retinal vessels. More reliable, and indeed as Foster Moore states, pathognomonic of hypertension, is the variation in vessel calibre from place to place which may be seen. He believes that when this is present, a high or very high degree of hypertension exists.

There is hardly space to list all the possible changes in the retinal vessels in hypertensive vascular sclerosis, as for instance pipe-stem sheathing and tortuosity of the vessels. In this latter condition it is to be remembered that the very wide range of tortuosity of the retinal vessels seen in normal eyes detracts greatly from the value of such an observation.

Secondary Retinal Changes—It is in the group of benign hypertension with considerably raised blood pressure and marked vascular sclerosis that the secondary changes in the retina are seen.

The retinal hæmorrhages are small, sometimes so small as to require much searching to find them, and are commonly in the nerve fibre layer, on this account being often flame-shaped. They are, of course, not unique to hypertension and are believed to result from an anoxia of the capillaries, the integrity of whose walls becomes impaired, allowing formed elements of the blood into the substance of the retina. This explains their fine and minute nature and it is interesting that the small retinal hæmorrhages sometimes seen in anæmia are of a similar type.

The combination of hard white exudates and retinal hæmorrhages was first given the name of "Arterio-sclerotic Retinitis" but it is now known that the changes are not inflammatory in nature and that the term "Retinitis" is a misnomer. The hard white exudates are small collections of hyaline material in the outer molecular layer of the

retina and by carefully drawn maps and painstaking observation Moore watched them disappear, leaving no trace, while others made their appearance. Like the retinal hæmorrhages, they are not peculiar to hypertension, but may be seen in other conditions. They have only significance, as far as hypertension is concerned, in the presence of vascular sclerosis, and have been noted to evolve in cases previously showing vascular sclerosis alone. They are small in size and sparse in distribution and are ophthalmoscopically in sharp contrast to the retinal œdema and patches of soft exudate seen in malignant hypertension.

Varied opinions have been expressed about these retinal changes. They were shown to belong to the picture of hypertension and not to general arterio-sclerosis, and Foster Moore and Gunn showed them to be part of the severe vascular sclerosis of the retinal vessels with hypertension of the benign sort as opposed to the acute angiospastic retinal changes of malignant hypertension. The former writer thought they were incidental to the vascular sclerosis, and it is now generally held that they are in themselves of no special significance and that the severe vascular sclerosis which they accompany is the important guide to the severity of the hypertension present.

Retinal hæmorrhages were seen in 5 cases and, as mentioned, they were small and sparse in distribution and occurred in the presence of well-marked vascular sclerosis and hypertension. It will be seen that they were present in cases which had average blood pressure very similar to the average values found in those cases which showed marked sclerosis alone, and tend to show that they are probably no different from the cases in this group.

Retinal "Complications" of Hypertensive Arteriolar Sclerosis — Any group of cases, such as the present, seen in an eye department inevitably includes a disproportionate number of what might be termed the ocular complications of the vascular sclerosis of hypertension, and they are of interest for the light they throw on the pathological changes of the disease. It is noteworthy that their occurrence is confined to the group in which there is a more severe degree of vascular sclerosis, as shown by the arterio-venous crossing changes, and moreover they are most frequent where those changes are most severe.

It is generally believed that tonic spasm of arterioles is responsible for the attenuation of the retinal arteries in hypertensive cases, and I have referred to the difficulty in assessing change in calibre of these vessels. A considerable reduction in calibre can occur without giving rise to any impairment of the visual function of the retina, however, periods of more intense vascular spasm occur, which are severe enough to interfere with retinal function, so that the patient experiences some loss of vision. Two such cases were seen in the group examined, and some details of one may be instructive.

The first was a married woman of thirty-eight, with a fair degree of retinal vascular sclerosis and a resting blood pressure of 170/110. For five years she had experienced transient loss of vision in one eye,

the vision remaining away for about four minutes on each occasion. She was seen first when the vision in the eye had remained away for six hours, and at the end of that time some returned, but the lower visual field, bounded by the horizontal meridian, remained completely blind. There was a reduction in calibre in the retinal vessels by comparison with those in the other eye, and the upper temporal division of the artery showed, some way from the disc, a localised area of acute spasm. No apparent change in this was brought about by rest and intra-venous hexamethonium, although some recovery in the visual field took place in the following days. Some months later there was no sign of the area of spasm although a small dense visual field defect was present. She was free from disturbance for some months, but recently she came again because of loss of part of the visual field, and on this occasion one of her retinal arteries, or more properly arterioles, showed 12 to 15 small areas of spasm so that the artery had the appearance of a string of sausages. Rest in bed for a day or two caused most to disappear, but one remained which has been present for two weeks. On this occasion, too, hexamethonium had no ophthalmoscopically visible effect.

This is a case in which the increase in arteriolar tone, suspected of playing an essential role in hypertension, became at times so severe as to give rise to functional upset in the tissue supplied by the vessels and finally complete cessation of function in a small region.

Five cases of thrombosis of the central retinal vein or one of its tributaries were seen. Coats and others are in agreement that this occurs most frequently in the presence of retinal vascular sclerosis, and Moore found a marked degree of hypertension in 40 of 61 consecutive cases of those which he examined. The 5 cases in the series seen by me would be included in Group II of Keith, Wagener and Barker's grouping.

There is hardly space to deal with the other complications apart from noting their incidence in that group of so-called benign hypertension which is associated with marked arteriolar sclerosis and a correspondingly high degree of hypertension. The vascular changes, the occasional incidental retinal changes and those I have classed as complications occurred in the type of hypertension classed by Volhard and Fahr as benign and by Keith, Wagener and Barker in their second group.

ACUTE ANGIOSPASTIC RETINOPATHY —The relationship of kidney disease to hypertension is essentially outwith the scope of a lecture by an ophthalmologist and appears indeed to be the subject of much speculation. It was early recognised that severe retinal changes were seen in association with chronic glomerulo-nephritis. These changes were gross œdema of the optic discs, exudates of a particular type into the retina and very marked constriction of the retinal vessels.

Because of the association with kidney disease and albuminuria, the name of albuminuric retinitis or neuro-retinitis was given to include the changes at the nerve head. Allbutt, however, was the first to realise

that a similar state of affairs could exist in the retina, without, for a time at least, evidence of severe kidney disease or albuminuria, and attention became directed to the invariable feature of severe hypertension which all cases showed. Fishberg made similar observations, showing that in all patients, without exception, with the changes now called malignant hypertensive retinopathy, the blood pressure was high and in the few in whom this was not the case the pressure had dropped because of cardiac weakness or the process was regressing. Volhard and Keith, Wagener and Kernohan showed, too, that this type of retinal change could occur in cases in which there was no clinically demonstrable renal change and in whom post mortem revealed only essentially vascular lesions of the kidneys. The unsuitability of the term albuminuric retinitis was further evident when Volhard showed that the changes were related to the spastic changes in the vessels and suggested the term acute angiospastic retinopathy. The changes were seen in patients who were already severely ill, or usually became so, in contrast to the more benign form of hypertension whose retinal changes have been discussed. Volhard and Fahr classed this as malignant hypertension and, as mentioned already, Keith, Wagener and Barker subdivided this to form their groups three and four of hypertension.

All surveys of such cases, showing the changes of malignant hypertensive retinopathy, indicate its frequency in a much younger age group than that in which the retinal changes of benign hypertension are seen. Keith, Wagener and Barker, who have the biggest series I could find, are typical, the average age in their groups three and four being forty-two and forty respectively. In the cases under review I found the average age to be forty-six.

Earlier writers believed the fundus picture varied in those cases of malignant hypertension without antecedent kidney disease and those with. Fishberg, who has studied this matter in detail, believes that there are many instances in which ophthalmoscopic differentiation between the malignant phase of a hypertension previously benign and that associated with a glomerulo-nephritis is impossible. The œdematous changes may be present in addition to the retinal vascular sclerosis of a hypertension previously benign, or the vascular sclerosis may be so slight that the œdematous changes occur in a fundus whose vessels are apparently normal except for their extreme attenuation in calibre by spasm. The same has been found to be true of those cases of malignant hypertensive retinopathy in whom antecedent kidney disease is recognised, previous vascular sclerosis may or may not be present.

On looking at a fundus, showing the changes of malignant hypertension retinopathy, one is struck by the œdematous appearance of the tissues, the retinal texture is altered and the reflex of the ophthalmoscope light is different, lines of apparent tension may make their appearance, giving the retina a watery, œdematous look. In the loose tissues around the disc this is especially seen, where the

TURNER'S SYNDROME IN A MALE INFANT

By THEODORE JAMES

(From the Duchess of York Hospital for Babies, Manchester)

IN 1938 Turner described a syndrome which he had observed in 7 unrelated females whose ages ranged from fifteen to twenty-two years. He published the syndrome under the heading "A Syndrome of Infantilism, Congenital Webbed Neck and Cubitus Valgus". This triad occurs often enough to give it a distinctiveness. The webbing of the neck, which varied from slight to marked in Turner's cases, gave the neck only an apparent shortness for there was no skeletal fusion or absence of cervical vertebræ. This apparent shortening had an accompanying low hair-line on the back of the neck which had no noticeable limitation of movement. There was no mental deficiency. A constant finding, but variable in degree, was a cubitus valgus, or an increase in the carrying angle of the elbows, and all 7 cases presented osseous and sexual retardation of development which Turner thought comparable with that of hypopituitarism. Roentgen study of the bones did not show any gross deviation from the normal. Treatment with pituitary growth hormones was without effect, but there followed a definite genital development after anterior pituitary gonadotropic hormone in 2 cases.

Since Turner's descriptive paper which did much to establish the syndrome it is being more frequently recognised, and more than 100 cases have appeared in the literature on both sides of the Atlantic. However, the first case of the syndrome in a male to be reported was diagnosed in 1943 by Flavell. His case was aged twenty-one years and was serving satisfactorily in the Royal Air Force. The intelligence was normal but the physique was below average. There was quite marked webbing of the neck but no real shortening. A cubitus valgus was present and a kyphoscoliosis associated with a prominence of the sternum. There was also a third degree bilateral claw-foot. The beard was scanty, there was no axillary hair and the pubic hair had a female distribution. The penis was of normal size but the testes were hypoplastic, despite which erection and emission were normal. In addition there was a failure of union of the fifth cervical neural arch.

The second case report of the syndrome occurring in a male was by Dorff, Appelman and Liveson (1948). Their patient was only three years old. There was webbing of the neck, shortness of stature, an enlarged head and genital underdevelopment. Mental development had been average since birth, and the usual "milestones" had been passed at an average rate of progress. A cubitus valgus was suspected.

(*sic*) There was no hair on the body but much fatty subcutaneous tissue of the breast, accompanying a deformity of the front of the thorax. A murmur was audible all over the precordium. Bilateral pes planus and an overriding toe on the right foot were present. Roentgenologic examination revealed a spina bifida bone defect between the last lumbar and upper sacral segments. There was some delay in the development of the carpal bones. *There was no perceptible urinary excretion of gonadotropins on 2 assays*, that is, there was no increase in the follicle-stimulating-hormone (FSH), which is contrary to the usual finding in females.

In the same year (1948) Greenblatt and Nieburg reported 2 cases of Turner's syndrome, one of these being a coloured male thirty years of age, whose height and weight corresponded with the upper limits of an eleven-year-old child. He showed webbing of the neck, a marked carrying angle (cubitus valgus), slight talipes varus, poor muscular development, moderately poor beard, small testes with atrophy of the left. The penis was described as "very large" and the illustration accompanying the case report leaves no doubt about this paradoxical and confusing feature. There was no evidence of heart disease or coarctation of the aorta. A biopsy of the right testis revealed a hypoplasia of the seminiferous tubules, azoospermia and a relative increase in the interstitial cells. Two urinary 17-ketosteroid estimations were at the low level of normal range, and serum gonadotropin assays showed no increase. These hormone assays did not help to explain the huge phallus.

In 1949 Reforzo-Membrives, Trabucco and Escardo gave a very detailed case report of the syndrome in an Argentinian boy aged ten and a quarter years. This case report also included the findings of a testicular biopsy. The child's height was below average, the abdomen was large, the skin smooth and there were many naevi on forehead, nose, neck and thorax. This latter finding is not uncommon in the female but this case of Reforzo-Membrives *et al* is the only case so far reported to show this skin anomaly in a male. Their case also showed a kypho-scoliosis, cubitus valgus, a largish head and an impression of bilateral epicanthus. The neck was webbed. The thorax was deformed and the heart had a systolic murmur at the apex. The penis was small and the scrotum small with few folds. The testes were small also but in the scrotum and were normal to palpation. There was hypotonia of muscles and flat-feet. The mental level was close to subnormal. The 17-ketosteroids were less than the normal average and no FSH was detectable on repeated examinations.

The fifth and latest case report of Turner's syndrome in a male that I have been able to collect, is one reported by Cunningham and Harley in 1951. Their case was aged seven years. The stature was short, the head relatively large, there were flat-feet, pterygium colli, underdeveloped penis, cryptorchidism. There was a bilateral slight ptosis and moderate cubitus valgus. Intelligence was at the low level.

of normal The 17-ketosteroids in the urine were estimated to be 11 mg per twenty-four hours when assayed, and the gonadotropins 6 mouse units

The following is the youngest male case to be reported

CASE REPORT

M H, No 27/269, a male infant was aged two years and three months when he was referred for a second opinion by request of the parents The chief complaint was one of failure to grow physically and mentally

Family History —Both parents were alive, young and well There was one sibling, a sister, aged four years, who was living and well in every way The family background was non-contributory The mother had had only two pregnancies

Past History —From the mother's account of her pregnancy when she was carrying M H there was good reason to believe that she suffered from a polyhydramnios, but she contracted no illnesses during that time She felt well in herself and brought this pregnancy, her second, to term The patient was born at home, and although the birth itself took place normally the baby's first cry was not heard until several hours later, and in the night of the birthday the neonate vomited what, to the mother, appeared to be swallowed amniotic fluid This vomiting caused the baby to choke, and the mother added the remark that fluid seemed to come from every orifice of the baby's body The birth weight was 8 lb 6 oz (3.8 kg)

There was difficulty in feeding the patient from the very beginning, both breast and artificial feeding were unsuccessful From the age of three months the patient attended the out-patient department of a hospital in its home-town because of this feeding difficulty, and continued to attend there for twelve months, but not much progress in management of the feeding of the patient could be made It was about this time that congenital disease of the heart in M H was first diagnosed During this time, also, it had become borne in upon both parents that there was evidence of physical and mental retardation manifesting in their second child M H was eighteen months old before he could sit up unaided, but his first teeth erupted at six months of age and the set of milk teeth was completed in the usual time There was no distortion or evidence of disease of these teeth which were, however, rather widely spaced

The patient had not contracted any illness, nor suffered any accident or operation No vaccination or immunisation procedures had been carried out on him

When M H was fifteen months old the family transferred their domicile and sought further advice about their son's failure to thrive A diagnosis of primary amentia associated with congenital disease of the heart was made and the parents advised accordingly A half-

hearted trial with thyroid extract was attempted but not persevered with when no rapid response was evoked

Adequate nutritional intake by the patient still remained a subsidiary problem for the parents when he was brought to this hospital

Physical Examination —The patient was a white male child whose age was two years and three months. His temperature, respiration and pulse were normal. His length was 80.0 cm (32 in.), sitting height 53.7 cm (21.5 in.), sitting height index $\left(\frac{\text{sitting height}}{\text{full length}} \times 100 \right)$ 67 per cent, head circumference 46.2 cm (18.5 in.), chest circumference 52.5 cm (21 in.), abdominal circumference 42.5 cm (17 in.), and weight 11 kg (24 lb 2 oz).

General Appearance —The first impression was that the child was well nourished, but closer inspection revealed a marked flabbiness of the subcutaneous tissue. The child was quite placid until examined, when he whined and resented the examination continuously, but otherwise he was in no distress. His colour was fair and his cheeks pink. A strong suspicion rested that the patient presented a syndrome, the facies were neither mongoloid nor cretinoid, but mental retardation was evident. The mouth tended to remain open and the tongue to protrude and the child persistently scratched his skin.

Skin —This was cool and without blemishes of any kind but was remarkably dry although it was capable of perspiration. Except for the dorsal aspect of the trunk, however, where there was a fine lanugo-like hair the skin was hairless. Skin elasticity was greater than normal. By bending the neck laterally to either side it was easy to bring out the folds of a latent pterygium colli, and traction of the skin over the mastoid processes produced a striking webbing of the neck (see Fig. 1).

The Lymph Nodes showed no abnormality.

Head —Although the head appeared relatively large when compared with the rest of the body its circumference (46.2 cm) was less than average (49 cm). The fontanelles were closed. There was no bossing or cranio-tabes of the skull. The hair of the scalp was plentiful, fair, of fine texture, and the occipital hairline came low. The skull was brachycephalic in its configuration.

Eyes —These were not prominent, there was no suggestion of hypertelorism, mongoloid slant, epicanthic folds or ptosis of the eyelids. The pupils were equal, round, of moderate size and reacted to light. There was no nystagmus nor strabismus and ocular movements were normal. Funduscopy was normal and the only abnormality determined was a considerably short optic axis.

The pinnae of the *Ears* were not deformed but were set rather low on the head.

The Nose presented a flattened bridge which was a little broader than average, but there was no nasal discharge and the airways were patent.

The Mouth had a complete set of slightly stained, rather widely

spaced milk teeth which were otherwise normal in appearance. The lips were full, the tongue, with several deep grooves, tended to protrude with salivation, but was of normal size, the gums, mucous membranes, palate, fauces and tonsils and pharynx were normal to inspection.

The Neck was not short and was freely mobile. It was broad from side to side, but pterygium was not apparent without adopting the manœuvre previously described.

The Chest—There was some depression of the lower sternum but no signs of scurvy or rickets. There was no precordial bulging but there was an excess of mammary fatty subcutaneous tissue (see Fig. 2).

The Lungs were normal to percussion and auscultation.

The Heart—No impulse was visible nor thrill palpable, nor was there clinical evidence of enlargement, but on auscultation there was a grade III systolic bruit audible all over the precordium but not between the scapulæ. The radial pulses were equal in tension and rhythm and the femoral pulses readily palpable. It was not practicable to measure the blood pressure.

The Abdomen—The spleen tip was palpable, but not the liver edge, and no other masses were palpable except costive fæces in the large gut. There was evident some muscular weakness of the anterior abdominal wall in the right inguinal region.

The Genitalia—The penis was small (2.5×1 cm) with a complete prepuce enclosing the glans, but the external urethral orifice was placed so as to present a slight degree of hypospadias. The scrotum, although rugose and dusky was rudimentary and empty. Both testes were of normal size and shape and of normal consistency but situate just over the external inguinal rings from where they could, by manual traction, be pulled into the scrotal sac. When they were released from this position, however, they would fly back to their former position and at times disappear altogether down the inguinal canals.

The Spine in the sitting position showed a mild degree of scoliosis which could be attributed to a slight deficiency of muscle tissue of the erector spinæ muscle of the right side. This deficiency was palpable. Flexibility of the spine was full in all directions. The coccyx was clinically abbreviated, the tip being 3 cm from the posterior margin of the anus. There was a deep dermal sinus overlying the coccyx but without any apparent attachment to the deeper structures. From this there was no exudation.

The Upper Extremities—These were of normal length and conformation. The range of active and passive movements did not appear lessened, but muscle power was not good and all joints showed an abnormal increase in flexibility, extensibility and other associated movements (see Fig. 3). There was no obvious cubitus valgus but there was an abnormal laxity of the joints so that it was easy enough to place both elbows in a marked degree of cubitus valgus passively. The fingers tapered and there was a slight webbing of the middle



FIG 1—This shows the webbing of the neck produced by slight traction on the skin over the mastoid processes



FIG 2—The depression of the sternum, excess of fatty subcutaneous tissue and cramping of the toes are obvious

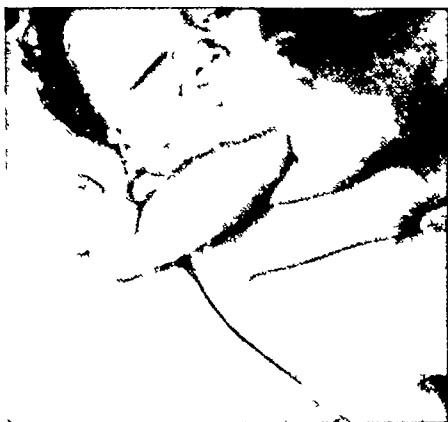


FIG 3—Illustrative of the excessive range of joint movement common to all joints



FIG 4—The hypotonia readily permitted the demonstration of the potential flat foot

and ring fingers bilaterally and a slight medial curving of each index finger

The Lower Extremities likewise, showed abnormal degrees of mobility of all joints and tended to be rather spindle-shaped but otherwise of usual configuration, except for the feet where the toes had a cramped appearance. On the right foot the great toe and fifth toe were almost in juxtaposition underneath and on the left foot there was an underriding of the fourth toe which also brought this toe close to the great toe—both feet appeared as though they had been laterally compressed. There was a severe potential degree of flat foot (see Fig. 4)

Nervous System—The mentality appeared dull and the sensorium clouded but there was no doubt that the patient was aware of his environment. However, there was no pattern of neurophysiological integration exhibited. All the deep tendon reflexes, despite the generalised hypotonia, were readily elicited and showed no asymmetry of responses and there were no abnormal nervous reflex mechanisms.

Laboratory Data—The hæmoglobin was 8.4 per cent, erythrocytes, 4.24 million, white blood cells 7000 with a differential count of polymorphonuclear leukocytes, 40 per cent, lymphocytes, 54 per cent eosinophils, 3 per cent, monocytes, 2 per cent, and Turk cells, 1 per cent. The routine urinalysis was normal and there was no detectable phenylpyruvic acid in the urine. The serum inorganic phosphorus was 5.9 mg per cent, the serum chloride 6.46 mg per cent as NaCl, serum calcium 8.5 mg per cent, serum potassium 19.8 mg per cent alkaline phosphatase, 16.2 K.A. units, serum cholesterol 155 mg per cent.

A fasting blood sugar level was 85 mg per cent and a glucose tolerance test (using about 15 gm of glucose, the patient resented the glucose) gave 100 mg per cent after half an hour, 80 mg per cent after one hour and 75 mg per cent after two hours.

On 25th to 26th November 1951, urinary excretion of 17-ketosteroids and gonadotropins were assayed. 17 ketosteroids 3.6 mg per litre or 1.6 mg per twenty-four hours and the gonadotropins were 8 mouse units per litre or 3.5 mouse units per twenty-four hours.

The Wassermann reaction and the Kahn precipitation test gave negative results and the tuberculin skin test (1:1000 dilution) was also negative. An electrocardiographic tracing did not point to any cardiac abnormality. A radiological skeletal survey did not show any changes from normal configuration except for some evidence of osteoporosis in the long bones of the lower extremities.

COMMENT

It is proper to give consideration to the extreme youth of this patient in evaluating the clinical features present in this case. At a first glance Turner's triad is not prominent, but careful examination

disclosed not only a retardation of general physical and genital development but the readily demonstrable presence of the webbing of the neck and potential cubitus valgus. The latter condition when fully manifested is dependent upon growth of the medial epicondyle of the humerus, and until osseous growth, however slow, does take place the cubitus valgus will remain latent but allowed for by the laxity of the ligamentous joint structures. Probably, this was what Dorff *et al* implied when they used the word "suspected" in connection with cubitus valgus in their young patient of three years.

Beyond Turner's triad, however, this case demonstrated quite a number of associated clinical features, such as the hypotonia, excessive range of movement of all joints, digital anomalies, almost hairless skin, congenital defects of the heart and a mental retardation which might not be synonymous with mental deficiency.

The hormone assays were confirmatory of the syndrome.

DISCUSSION

There is good evidence that this syndrome had not gone unnoticed before 1938 when it was so prominently brought to the attention of endocrinologists and gynæcologists by Turner.

Ullrich (1950) stated that, from developmental and phenotypical points of view "the asymmetrical form of the Status Bonnevie-Ullrich corresponds entirely with the anomalous complex of *my*-mice engendered in embryos of the Bagg-Little mouse by the mechanism of wandering cerebro-spinal fluid blebs discovered by Bonnevie. The typical complex of abnormalities with pterygium colli is, as the symmetrical form of the Status Bonnevie-Ullrich, identical with the syndrome of infantilism, webbed neck and cubitus valgus described by Turner in 1938. In this complex of developmental abnormalities the symmetrical distribution of all the defects makes the syndrome incompatible with the wandering bleb mechanism, which, also, cannot satisfactorily explain the infantilism connected with it, and the obvious gynæcotropy. Embryonic foetal swellings of the skin, however, which in this syndrome are probably of autochthonous origin, must account for the greater part of the abnormalities of the Turner syndrome just as in the asymmetrical condition."

Funke (cited by Rossi and Caflisch, 1951) in 1902 was the first to describe a case of webbed neck and sexual infantilism so closely allied, if not identical, with Turner's syndrome.

Rossi, Caflisch and Angst (1950) in order to show the aetiology and pathogenesis of the multiple malformations grouped under the eponyms of Ehlers-Danlos syndrome, Turner's syndrome, the Status Bonnevie-Ullrich, and arthromyodysplasia congenita (multiple congenital articular rigidities) emphasised the analogy of these affections with those observed by Bonnevie in the rat. In this latter connection there was a display of microphotographs demonstrating an "area

membranacea superior" in man which might possibly be the equivalent of the anterior foramen of Weed through which the cerebro-spinal fluid, in the rodent, passed into the subcutaneous tissue. One of the conclusions to which these authors came as a result of a clinical study of 4 cases of the Ehlers-Danlos syndrome, 20 of pterygium colli and 9 of arthromyodysplasia congenita in their own experience, and a further study of other cases in the literature, was that Turner's syndrome is identical with the Bonnevie-Ullrich syndrome.

The lack of terminological exactitude for the condition under discussion justifies, perhaps, an extension of the eponymous designation to "the Bonnevie-Ullrich-Turner syndrome" which does draw attention to the degrees of variation possible for the syndrome.

Rossi and Caflisch (1951) reviewed 177 cases in the literature and 20 of their own cases showing multiple malformations associated with pterygium formation, and they suggested that the classical picture should be referred to as the "pterygium syndrome". They observed that certain malformations occur regularly in most of the cases and allow a sub-classification into 5 main groups: the bilateral Ullrich syndrome, dystrophia brevicollis congenita (Nielsen), pterygo-nuchal infantilism (Turner), unilateral Ullrich syndrome, and congenital pterygo-arthromyodysplasia. However, the only deduction they make with any feeling of certainty is the presence of a hereditary factor determining the anomaly. These authors grouped together all conditions which manifested a pterygium whether of neck, axilla, knee or fingers and whether in the typical or abortive form.

Albright, Smith and Fraser (1942) in a paper which contained descriptions of 11 cases of a syndrome characterised by primary ovarian insufficiency and decreased stature, went into some detail and tabulated 11 points which their cases brought out for consideration. These 11 points included references to the short stature, infantile genitalia, scanty pubic hair, retardation of bone age, a constant increase of FSH, a lower than average normal of 17-ketosteroids, response to oestrin therapy, the insulin tolerance test, and associated other congenital anomalies. These authors were inclined to regard Turner's similar series of cases as a sub-form of the syndrome they were describing. Among the associated congenital anomalies they found webbing of the neck, and coarctation of the aorta especially frequent.

Ezes, writing in Algiers in 1949 mentioned 6 cases of Turner's syndrome in females which had appeared in the French literature. He noted the not uncommon presence of pigmented naevi which Reforzo-Membrives *et al* found so conspicuous in their male child patient, a shortness of the fourth metacarpal, a slight epicanthus, bilateral genu valgum, coarctation of the aorta, and absence of the spheno-occipital suture. He had found recorded in the literature, autopsy evidence of absent mesenteric vascular arcades, a constant hypoplasia or aplasia of ovaries and hypomorphosis of the adrenal cortices.

In the female the syndrome *almost* always includes an increase in the pituitary gonadotropins which accompanies the ovarian insufficiency. The features of dwarfism, increased urinary gonadotropins, decreased 17-ketosteroids, are not absolutely constant findings, and as Reforzo-Membrives *et al* say, this lack of uniformity in the elements of the syndrome raises the problem of pathogenesis and weakens the contention of Albright *et al* that the absence of ovarian oestrogens diminishes the stimulus for the production of androgens by the suprarenal cortex. This decrease shows as a low value for the 17-ketosteroids, which might be the reason for the defective growth. It is difficult to reconcile this theory with the existence of the syndrome of "rudimentary ovaries" in patients with a normal or even increased 17-ketosteroid level (Del Castillo, cited by Reforzo-Membrives *et al*). Most authors are inclined to believe that the association of "rudimentary ovaries" with defective growth is due to genetic factors (Ezes), Dorff *et al* believe a slight alteration in the hypophysis could account for delay, retardation, or stunting of growth, but because of their failure to prove the presence of hypophyseal gonadotropins in the urine of their patient, they could not attribute to a diminished function of the testes the same importance which is given to the ovaries in the pathogenesis of the syndrome, which was the reason for the differential diagnosis between their case and hypophyseal dwarfism not being obvious and a fundamental difference between cases of "rudimentary ovaries" and their case, that is, a lack of the hypophyseal gonadotropin in the urine of their patient after repeated search. They suggested two explanations for this discrepancy either a primary testicular insufficiency without an increase in hypophyseal gonadotropins or, a gonadal insufficiency which could be the result of a congenital hypophyseal disturbance, perhaps a predominant deficiency of the gonadotropins leaving the other hypophyseal functions less affected. Dorff *et al* also regarded the absence of urinary excretion of gonadotropins in their case as being compatible with the age (three years) of their patient and the production of hormone as being likely to take place at the age of puberty. Reforzo-Membrives *et al* give some support to this opinion. They too, found no FSH in their case on repeated examination and the 17-ketosteroids were less than the average normal, and they cite Talbot when they state that available data indicate that gonadotropins are not detectable in the urine of normal boys before the twelfth year of life.

These observations give considerable significance to the finding of gonadotropins in my case, 8 mouse units per litre or 3.5 mouse units per twenty-four hours represents a marked increase in this hypophyseal hormone and the determination of 3.6 mg per litre or 1.6 mg per twenty-four hours for the 17-ketosteroids, a marked decrease. This tallies well with the endocrinological assays which have been shown to be usual in the female with the syndrome. These hormonal findings in my case positively exclude it from those of hypophyseal origin.

The subject of this report not only presented Turner's triad but also several other outstanding clinical features. There were a deformity of the chest, a postural scoliosis (due to a deficiency of the right erector spinæ muscle), a congenital defect of the heart, a marked increase of joint movement beyond the normal range and a mental retardation or deficiency accompanying an unusual peculiarity of the facies.

Rossi and Caflisch (1951) make a statement of much import which demands agreement on the identities of the 5 syndromes which at intervals have been reported in the literature and which they have grouped together. Should their thesis find general acceptance, then the impression prevailing at the present time that Turner's syndrome in the male is a great rarity will fall away and there no longer will be a call for the special mention which it now receives.

They write as follows: "Nous n'avons jusqu'ici fait état que du sexe féminin parce que le syndrome de Turner a été décrit presque exclusivement chez les femmes. Cependant une analyse minutieuse de la littérature nous a permis de noter la présence de ce syndrome également chez l'homme. En effet, nous avons trouvé 13 fois une cryptorchidie bilatérale ou unilatérale avec atrophie de l'autre testicule ou plus rarement d'autres malformations génitales, comme l'hypospadié ou le scrotum bipartit. Nous avons fait 3 observations analogues chez nos enfants dont les testicules étaient insuffisamment développés tandis que le pénis était normal." Such a statement negates the care which has been taken by writers who have studied cases of Turner's syndrome, to exclude such conditions as the Klippel-Feil alone, or the dystrophia brevicollis congenita of Nielsen which includes the Klippel-Feil structural anomaly of the cervical vertebrae.

An observation which I have not met with in the relevant literature, but which has quite strikingly entered my experience, is the extraordinary similarity of the facies of the 3 infant cases of Turner's syndrome which I have seen. The other two infant cases were females and the diagnosis for the second female case was suggested by its likeness to the first case, already diagnosed, and my male infant so closely resembled the other two that Turner's syndrome was immediately advanced as a working diagnosis.

SUMMARY

The few male cases of Turner's syndrome which have appeared in the literature as such, are reviewed.

Another male case of the syndrome, the youngest that I know of, is presented.

A discussion gives consideration to different interpretations of the syndrome in the female. These have been propounded by different authors, and where the syndrome in a male has shown a discrepancy from the syndrome as it occurs in the female, the responsible author's comment has been added.

Notice is drawn to an opinion expressed by the authors of one paper in which it is stated that the widely held understanding that Turner's syndrome occurs almost exclusively in females, is in error

I wish here to thank Mr G Ward, the hospital photographer, for the photographic illustrations

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OBITUARY

SIR DAVID WALLACE, K B E , C M G , L L D , F R C S E

THE oldest of Edinburgh surgeons passed away at his Edinburgh residence on 21st April within three months of his ninetieth birthday David Wallace, who came of a Fife family, was born in 1862, son of David Wallace of Balgrummo His school education was at Dollar Academy, from which he entered Edinburgh University, and graduated M B , C M in 1884 During the next year he was house surgeon in Edinburgh Royal Infirmary to Professor John Chiene, and house physician to Professor John Wyllie With one exception, all his fellow residents are now dead From the outset he aimed at a surgical career, and by 1886 he had obtained the qualification of M R C S Eng , and a year later that of F R C S E In 1892 he was appointed assistant surgeon in Edinburgh Royal Infirmary, where for some years he was assistant to Professor Chiene, to whom for a time he was also private assistant Previously he had followed the frequent Edinburgh surgical custom of holding a demonstratorship in the University Department of Anatomy In due course he was in charge of wards as surgeon from 1908 to 1923 for the usual period of 15 years, after which he became consulting surgeon After leaving the Infirmary he was for many years visiting surgeon to Longmore and Liberton Hospitals for Incurables , and he took a prominent part in the management of the Princess Margaret Rose Orthopædic Hospital at Fairmilehead

Sir David was involved in military surgery in the South African War, as he was in charge of the expeditionary Edinburgh Hospital, of which, in association with Mr George Chiene, he wrote the Report , he was mentioned in despatches, received the medal and clasp, and was appointed C M G In 1908, on the formation of the Territorial Force, he, along with the more senior surgical members of the Infirmary, was included in the staff of the 2nd Scottish General Hospital, and they were mobilised in August 1914 He had, however, played an important part in the formation of an Edinburgh branch of the Red Cross Society in 1908 , and indeed he was ultimately secretary or chairman for over thirty years It was rightly considered in the first war that his services would be of greatest value in this sphere, and he was appointed Commissioner of the Red Cross for the south-eastern district of Scotland This was a much more difficult position than an ordinary army command Among other duties there fell to him the organisation and supervision of the numerous Red Cross convalescent homes, many of which were large mansions generously offered by their owners, and he was very successful in meeting the wishes of the owners where possible and in showing firmness where essential, without giving offence For his services he was appointed C B E in 1918 and K B E in 1920 , and he retired from the Territorial Army with the rank of Brevet Lieutenant-Colonel

Sir David was an example of the best type of surgical specialist, an excellent general surgeon with special interest in one branch of surgery In his case this was urology, in which, encouraged in his earlier years by Professor Chiene, he was one of the pioneers in Edinburgh and an accepted authority , and this was recognised abroad by his election to the French Association of Urology

Among his other honours he was President of the Royal College of Surgeons

of Edinburgh from 1921 to 1923, and was its senior resident Fellow at the time of his death. He had been examiner in surgery and clinical surgery for the University of Aberdeen, was a Deputy-Lieutenant of the City of Edinburgh, and in 1930 the University of Edinburgh conferred upon him the honorary degree of LL.D. He contributed many articles on surgical subjects to medical journals.

Sir David was a successful teacher in his systematic class in the School of Medicine and clinically in the Royal Infirmary, where he always had a large class. He was clear and definite in his teaching, kindly to patients, possessed the valuable gift of a retentive memory for names and faces, and was popular with colleagues, students and patients. He was a good administrator, for he had a logical mind which led him to definite, often dogmatic, decisions. He would always listen closely and courteously to opposing arguments, but it was not easy to persuade him to change an opinion to which his logical thought had led him.

Sir David married a daughter of the late Sir Thomas Clouston, the eminent specialist in mental diseases, by whom he is survived. Lady Wallace, like her husband, is an excellent administrator, especially well known in relation to the Victoria League and the Queen's Institute of District Nursing, and in 1946 she received the honour of C.B.E. He is also survived by his two sons, neither of whom has followed the medical profession.

Sir David Wallace had outlived almost all his actual contemporaries, and during the last few years failing health had withdrawn him from most of his surgical interests, but he had intimate friendships with many men younger than himself, to whom his death is a real personal grief.

NOTE

At a Quarterly Meeting of the College held on Tuesday, 6th May 1952, the President, Dr W A Alexander, in the Chair, the following were elected Fellows of the College —
Royal College of Physicians of Edinburgh Ronald Foote Robertson, M B EDIN , John Taylor Randolph Russell, M D , EDIN

The following were elected Members of the College —Gostha Bihari Sinha, M B CALC , Sunder Balse, M B BOMB , Sanatkumar Hiralal Shah, M B BOMB , Graham Francis Hall, M B NZ , Michael John Bailey, M B CAPE TOWN , Sutchffe Ruttle, M D BELF , Deb Prasanna Basu, M B CALC , Bal Sitaram Kulkarni, M B OSMANIA , Neol Myddleton Mann, M D CANTAB , Douglas Telfer Kay, M B EDIN , Oliver Gordon Jones, M D LEEDS , Walter Bolliger, M B SYDNEY , Andrew Macfarlane, M B EDIN , Nathaniel Kemsley Pein, M B WITWATERSRAND , William Ian Forsythe, M D BELF , William Dawson Hamilton Conacher, M B GLASG , Anilkant Duleral Desai, M B BOMB , Zahur Hussain Nurullah Kadri, M D BOMB , Shanti Narain Mathur, M B OSMANIA , Robert Arthur Kershaw, M B MANC , Bermeshwer Prasad, M B PATNA , George Stewart Kilpatrick, M B EDIN , Roger John Connolly, M B SYDNEY , Kenneth Lamonte Stuart, M B BELF , John Alexander McLeod, M B OTAGO , Balbir Singh Khaira, M B CALC

NEW BOOKS

Psychosomatic Gynecology By WILLIAM S KROGER, M D , and S CHARLES FREED, M D Pp viii+503 London W B Saunders 1951 Price 40s

This volume stresses the importance of emotional factors in the etiology of obstetrical and gynæcological disorders, and indicates how the individual's personality may be assessed and treated. From an extensive bibliography, ranging mostly over the last thirty years, the authors have collected many varying viewpoints. To these they have added their personal opinions and supported them by illustrative case histories.

The authors are aware of the controversial and often speculative nature of some of the material presented, and constantly admit that the psychiatric approach is limited by such incompleteness of fundamental knowledge. Yet the practical importance of this subject is recognised, and in this volume will be found an interesting attempt to define the present stage of its development and therapeutic value.

The reviewer feels that making each chapter an essay, complete in itself, has resulted in tedious repetition. A more closely knit presentation and condensation would enhance another edition.

Fellowship Examination Papers, 1947-1951, For the Diplomas of the Royal College of Surgeons, Edinburgh Pp 50 Edinburgh E & S Livingstone 1951 Price 5s 6d net

Racing enthusiasts, football pool addicts, and examination candidates study form. This is the "form book" for the Fellowship. Aspirants should find it useful but should always beware of the dark horse.

The Diagnosis and Treatment of Intrathoracic New Growths By MAURICE DAVIDSON, M A , D M , B CH (OXON), F R C P Pp vi+260, with 170 illustrations London Oxford University Press 1951 Price 42s net

In this book Dr Maurice Davidson writes in a readable and pleasant way about intrathoracic new growths, illustrating his subject by extensive case histories and numerous radiographs. The book suffers from two misfortunes. It apparently went to press too late to include any mention of the recent British and American work demonstrating the association between heavy tobacco-smoking and carcinoma of the bronchus. Again, probably owing to delay in publication, the international nomenclature of the bronchi, which has been recently agreed, has had to be included only as an appended table. The diagram of the normal bronchi, shown in Fig 1, is presumably a tracing of a bronchogram and gives the mistaken impression that there are lateral communications between the bronchi: this should be altered in later editions. The chapter by Professor Smithers on radiotherapy is excellent but might with advantage have been twice as long, that by Mr O S Tubbs on operative treatment is an admirable summary, reflecting a wide personal experience and containing much of interest to the physician.

Hygiene, Infectious Diseases and Dietetics By DENNIS H GEFFEN, M D , D P H , and SUSAN TRACY, M R C S , L R C P , D P H Pp viii+276 London Longmans, Green & Co 1951 Price 9s 6d net

Two London teachers have written this book to cover the syllabus laid down for student nurses by the General Nursing Council. The authors hope that it will also be useful to students of social welfare. These aims are fulfilled well, and doctors called upon to lecture to nurses on these subjects will also find it valuable. The book covers practical problems which arise in Great Britain, but will be of little use to nurses in the tropics.

Summary of Legislation and Directory of Organisations for the Care of the Physically Handicapped Compiled by the Central Council for the Care of Cripples Pp xiii+139 London Heinemann 1951 Price 5s 6d net

The title is sufficiently comprehensive to make the book attractive to those who seek guidance on that subject and they will not be disappointed. The explanatory notes on the various Acts and organisations are concise and well written.

Surgical Practice of the Lahey Clinic By Members of the Staff of Lahey Clinic, Boston Pp xiv+1014, with 784 illustrations on 509 figures London W B Saunders 1951 Price 75s

This volume presents the practice of the Lahey Clinic, and while it is not intended to cover the whole field of surgery, the extensive practice of the Clinic provides material for a considerable number of its aspects. Naturally the treatment of thyroid disease has a large place, and the remainder of the book deals with the surgery of the œsophagus, lungs and heart, the stomach and duodenum, the small intestine, colon, sigmoid and rectum, the biliary tract, the spleen, adrenal gland and pancreas, the breast, the pelvis, the bones and joints, the brain, spinal cord and nerves, and anæsthesia. Dr Lahey points out in his introduction that many of the operative procedures have become standardised, and that he finds this useful both in the training of young surgeons and in the care of the patient. Whether the principle be accepted or not, the book contains the fruits of a large experience which has been dealt with by Dr Lahey and his colleagues in an exceedingly thoughtful manner. Some of the letterpress and some of the illustrations are repeated more than once from paper to paper (which should be unnecessary for standardised techniques), but this criticism apart, the volume will well repay perusal by even experienced surgeons whether or not they agree with the views and the procedures it describes.

NEW EDITIONS

Treatment by Manipulation By H JACKSON BURROWS, M D, F R C S, F R A C S, and W D COLTART, M B, F R C S Second Edition Pp 80, with 29 illustrations London Eyre and Spottiswoode 1951 Price 12s 6d net

Manipulation forms a small but important part of orthopædic treatment This is a small book in true perspective, not seeking like some to over emphasise its subject

Indications, hazards and methods are clearly described, but it is impossible to teach technique by printed word or still photograph For all its clarity this book does not achieve the impossible

Applied Pharmacology By A J CLARK Eighth Edition, revised by ANDREW WILSON, M D, P H D, F R F P S, and H O SCHILD, M D, P H D, D S C Pp vii+691, with 120 illustrations London J & A Churchill 1952 Price 37s 6d net

Ten years have passed since A J Clark's death a year after the publication of the seventh edition of his well-known textbook In view of the enormous advances in the subject in the interval the authors have had to revise the book completely and add new chapters The fundamental character of the book has been maintained, and, as before, pharmacology is presented on a solid foundation of physiology and pathology The only real change is the exclusive use of the metric system in the dosage of all preparations The authors are to be congratulated on maintaining the high standard of former editions, and the new "Clark" should prove as popular with students and practitioners alike as the original

Diseases of the Nose, Throat and Ear By I SIMSON HALL, M B, CH B, F R C P E, F R C S E Fifth Edition Pp vii+463, with 8 coloured plates and 82 illustrations Edinburgh E & S Livingstone 1952 Price 18s net

The early appearance of a further edition of this textbook is an indication of its well-merited popularity Designed for the practitioner and student, its general features and size are unchanged It has been brought thoroughly up to date, notably on the subjects of the physiology of the nose, the employment of antibiotics in acute otitis media and the treatment of Meniere's disease A special section is devoted to the use of the antibiotics The insertion of alternative metric dosage in the formulæ is a useful addition The price of this edition has increased only by 3s and it continues to be an admirable volume

A Synopsis of Hygiene (Jameson and Parkinson) By L ROBERTS, M D, M R C P, D P H, with the assistance of KATHLEEN M SHAW, M B E Tenth Edition Pp viii+891 London J & A Churchill 1952 Price 42s net

This "synopsis" first appeared thirty two years ago and rapidly established itself as a standard textbook for D P H students and a reference work for the M O H's office On Brigadier Parkinson's retirement, Dr Roberts, the M O H of Sheffield takes over the editorship, assisted by Kathleen Shaw of the London School of Hygiene and Topical Medicine The scope and style of the book remains essentially unchanged, and the new edition is a workmanlike mixture of the old hygiene and the new social science and legislation that go to make modern public health This edition presents an up to date account of public health practice in England to day The account of the great work of the World Health Organisation is, however, crammed into less than two pages Could the next edition have a more imaginative account of W H O's aims and achievements?

Warwick and Tunstall's First Aid to the Injured and Sick Edited by A P GORHAM, M V, M R C S, L R C P, D A Nineteenth Edition Pp 278, with 288 figures Bristol John Wright & Sons 1952 Price 6s 6d

Dr Gorham has brought this old established guide up to date in accordance with modern practice. The first eighty pages are devoted to an elementary account of anatomy and physiology essential for the first aider, and the remainder deals with various aspects of the subject, wounds, hæmorrhage, fractures, asphyxia, poisoning, unconsciousness and so forth. Descriptive details are more elaborate than in the average book of this sort and the copious illustrations are helpful and entirely adequate.

One of the best manuals of its kind

BOOKS RECEIVED

- CROSSE, V MARY, O B E, M D (LOND), D P H, M M S A, S (OBSTET), R C O G
The Premature Baby Third Edition (*J & A Churchill Ltd, London*) 16s net
- FISHER, JAMES T, M D, and HAWLEY, LOWELL S The Diary of a Psychiatrist
(*Medical Publications Ltd, London*) 16s net
- GREENHILL, J P, M D Surgical Gynecology
(*The Year Book Publishers Inc, Chicago, U S A*) 65s net
- GULLAN, M A, S R N Theory and Practice of Nursing Sixth Edition
(*H K Lewis & Co Ltd, London*) 18s net
- HARDY, JAMES D, M D, F A C S Surgery and the endocrine System
(*IV B Saunders Company, London*) 25s
- HARTWELL, JONATHAN L Survey of Compounds which have been Tested for
Carcinogenic Activity Second Edition
(*United States Government Printing Office, U S A*) \$4 25
- ISHIHARA, S, M D Tests for Colour Blindness Tenth Revised Edition
(*H K Lewis & Co Ltd, London*) 75s net
- JOHNSTONE, R W, C B E, M A, M D, HON LL D William Smellie
(*E & S Livingstone Ltd, Edinburgh*) 20s net
- KORNITZER, MARGARET Child Adoption in the Modern World
(*Putnam, London*) 16s net
- Edited by LEVY, ROBERT L, M D Disorders of the Heart and Circulation
(*Thomas Nelson & Son, Edinburgh*) 91s 6d net
- LOVATT EVANS, SIR CHARLES Principles of Human Physiology Eleventh
Edition (*J & A Churchill Ltd, London*) 52s 6d net
- MANSON BAHR, SIR PHILIP H, C M G, D S O, M A, M D, D T M, and H
(CANTAB), F R C P (LOND) Synopsis of Tropical Medicine Second Edition
(*Cassell & Company Ltd, London*) 15s net
- Edited by MONCRIEFF, ALAN, M D, F R C P A Textbook of the Nursing and
Diseases of Sick Children Fifth Edition
(*H K Lewis & Co Ltd, London*) 37s 6d net
- PEEL, ALBERT A FITZGERALD, M A, D M (OXON), F R F P S (G) Diseases
of the Heart and Circulation Second Edition
(*Oxford University Press, London*) 35s net
- Edited by PLUNKETT, RICHARD J, M D, and HAYDEN, ADALINE C, R R L
Standard Nomenclature of Diseases and Operations Fourth Edition
(*H K Lewis & Co Ltd, London*) 60s net
- SIMPSON, KEITH, M D (LOND) Forensic Medicine
(*Edward Arnold & Co, London*) 21s net
- WALSHE, F M R, M D, D S C, F R S Diseases of the Nervous System
Seventh Edition (*E & S Livingstone Ltd, Edinburgh*) 24s net
- WOLFF, WERNER The Threshold of the Abnormal
(*Medical Publications Ltd, London*) 30s net
- WOLSTENHOLME, G E W, O B E, M A, M B, B CH Ciba Foundation Col-
loquia on Endocrinology Volume I (*J & A Churchill Ltd, London*) 30s net
- S F A Catalogue of Medical Films (*Harvey & Blyth, London*) 15s net

Edinburgh Medical Journal

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ACUTE APPENDICITIS

By I E W GILMOUR, FRCSE, and A G R LOWDON,
OBE, FRCSE

(From the Department of Surgery, University of Edinburgh)

RECENT articles on appendicitis have drawn attention to the improvement in the last ten to fifteen years in the figures for morbidity and for mortality. In a review of 1265 cases treated in the Presbyterian Hospital of New York in the five-year period 1944-48, Schullinger (1950) reported a mortality of 0.94 per cent, compared with a mortality of 3.18 per cent in the whole period 1916-49. Cotter and Gebbie (1948) quote figures from Christchurch Hospital, New Zealand, in which, from 1942-47, 2489 cases of appendicitis were treated with a mortality of 0.76 per cent, in the years 1937-42, a series of 2122 cases from the same hospital showed a mortality of 1.7 per cent. Wakeley and Childs (1950) reported 217 appendicectomies performed without a death from February 1947 to August 1949, their article is prefaced by information procured by the Registrar-General for England and Wales, which confirms the fall in mortality in recent years.

Many factors are responsible for this improvement, earlier diagnosis, the introduction of chemotherapeutic drugs, improved anaesthesia and the more liberal use of intravenous fluids have all contributed towards the reduction in mortality. This review is an attempt to assess the relative values of these factors, and to find out how further improvement may be obtained, by comparing the results in two series of cases of acute appendicitis treated in the Royal Infirmary of Edinburgh during the two periods 1930-31 and 1948-50 respectively.

SELECTION OF CASES

The years 1930-31 and 1948-50 were chosen for this comparison because the advantages of modern anaesthesia, intravenous therapy and antibiotic drugs became established in the intervening period. The cases in 1930-31 were taken from the wards of Sir David Wilkie and Sir John Fraser, and the cases in 1948-50 were taken from the same wards under the charge of Sir James Learmonth.

The case records of all patients diagnosed as having appendicitis or treated by appendicectomy were reviewed and care was taken to

eliminate from both series all cases in which the diagnosis of acute appendicitis was not adequately established by operative findings or clinical progress the results of this selection are of incidental interest as evidence of changing surgical opinions and practice

Series A 1930-31 —From all the cases diagnosed as appendicitis in these years a small number of patients under twelve years of age was excluded because in the second period all such patients were admitted to the Royal Hospital for Sick Children The total number of cases reviewed was 745, 170 of these were interval appendicectomies or cases of "chronic appendicitis," and 40, diagnosed as acute appendicitis, had a normal appendix at operation The remaining 535 were accepted as cases of acute appendicitis

Series B 1948-50 —Consecutive cases from the beginning of 1948 were examined and selected in the same way until an equal total of cases of acute appendicitis was reached, thus all cases in 1948, 1949 and about nine months of 1950 were reviewed The smaller number of cases in these later years is probably accounted for by the fact that more emergency surgery is being carried out in the peripheral hospitals in the city and surrounding district The total number of cases was 681 Of these, 30 were interval or "chronic" cases and in 116 the appendix was normal the remaining 535 were accepted as cases of acute appendicitis

The change in numbers of chronic and normal appendices is of interest The smaller number of cases of "chronic appendicitis" in the later period is explained by the present reluctance to make this diagnosis The increase in the numbers of "normal" appendices removed is due to the more frequent recognition at operation of non-specific mesenteric adenitis

Further analysis is confined to the 535 acute cases in each period In both series the operations were performed by a number of different surgeons who were, with few exceptions, of the registrar grade

ANALYSIS OF CASES AND RESULTS

The mortality in Series A was 4.9 per cent, in Series B 1.1 per cent

Classification —For simplicity, four types of acute appendicitis have been distinguished —

- (1) Simple acute appendix inflamed, but not perforated
- (2) Perforated, with local peritonitis early localised peritoneal involvement
- (3) Perforated with general peritonitis inflammation spreading or generalised in the peritoneal cavity
- (4) Abscess localised intraperitoneal collection of pus from an appendicular lesion

An analysis of the total numbers and mortality rate in each type of appendicitis is given in Table I

The numbers for each type of appendicitis show a striking similarity. Comparison of the two series shows that the mortality has been reduced in all types of appendicitis, most strikingly in cases of abscess, and that in Series B fatal cases were confined to the group with perforated appendices.

TABLE I

Acute Appendicitis Classification and Mortality

Type of Appendicitis	SERIES A 1930-31			SERIES B 1948-50		
	Total	Deaths	Per cent Mortality	Total	Deaths	Per cent Mortality
Simple acute	392	4	1.0	403	0	0
Perforated local peritonitis	88	4	4.5	76	2	2.6
Perforated general peritonitis	36	13	36.1	35	4	11.4
Abscess	19	5	26.3	21	0	0
Total	535	26	4.9	535	6	1.1

Age in Relation to Mortality—The distribution of cases in age groups by decades is shown in Table II. The number of patients under forty years of age was 440 (82.2 per cent) in Series A, and 429 (80 per cent) in Series B.

TABLE II

Age Distribution and Mortality

Age in Years	SERIES A 1930-31		SERIES B 1948-50	
	Total	Deaths	Total	Deaths
12-19	195	5	203	
20-29	167	6	135	1
30-39	78	2	91	
40-49	40	3	43	
50-59	30	5	39	2
60-69	24	5	13	1
70-79	1		11	2
Totals	535	26	535	6

In both series the mortality was higher in the older age groups. The mortality in patients over forty years of age was 12.4 per cent in Series A and 4.7 per cent in Series B. In patients under forty years of age the mortality was 3.4 per cent in Series A and 0.2 per cent in Series B.

Sex in Relation to Mortality—In both series there were more males than females. Table III shows that in both series the incidence of perforation and the mortality were higher in males.

Duration of Illness before Admission in Relation to Mortality—Comparison of the two series in respect of duration of illness before

admission to hospital shows that there has been no important change (Table IV)

TABLE III

Sex Distribution, Incidence of Perforation and Mortality

Sex	SERIES A 1930 31					SERIES B 1948 50				
	Total	Perforated		Deaths		Total	Perforated		Deaths	
		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent
Males	291	81	27 8	13	4 5	280	83	29 6	4	1 4
Females	244	62	25 4	9	3 7	255	49	19 2	2	0 8

TABLE IV

The Relation of Mortality to Duration of Illness before Admission

SERIES A 1930 31					SERIES B 1948 50				
Number of Days before Admission	Number of Cases	Number with Perforated Appendix	Deaths	Per cent Mortality	Number of Days before Admission	Number of Cases	Number with Perforated Appendix	Deaths	Per cent Mortality
1	300	36	13	3 3	1	300	36	3	0 7
2	96	36			2	104	42		
3	45	17	13	9 3	3	53	25	3	2 3
4	25	18			4	25	11		
Over 4	69	36			Over 4	53	18		
Total	535	143	26	4 9	Total	535	132	6	1 1

The principal interest of this comparison appears to lie in the numbers of late cases with perforation on admission. The number of patients with perforation of the appendix and a history of four or more days' illness was 54 in Series A and 29 in Series B. This is a significant difference and might indicate that perforation is occurring earlier, but more probably shows that practitioners are recognising the development of peritonitis sooner.

It is noteworthy that perforation of the appendix occurred within the first twenty-four hours in 36 (6 7 per cent) cases in Series A and in an identical number in Series B, of these 9 (1 7 per cent) in Series A and 14 (2 6 per cent) in Series B had general peritonitis.

In both series the mortality rises with delay in admission to hospital.

TREATMENT

The following aspects of the management of the cases under review merit consideration: the effect of purgation before admission to hospital, and changes in the methods of treatment employed with

particular reference to drainage, chemotherapy, intravenous infusion, gastric aspiration, the management of abscess, and anæsthesia

Catharsis—Of the 1070 patients in the review, 99 had taken purgatives. Of these, 49 (49.5 per cent) had perforated appendices. Of the remaining 971 patients, 226 (23.3 per cent) were admitted with perforated appendices.

The estimate of the number of patients taking purgatives is based on the case records. The total is therefore the accountable minimum and it is probable that in both series there were unrecorded cases of purgation.

Drainage—The most striking change in technique is the recent tendency to omit peritoneal drainage when the appendix is perforated. In Series A the peritoneum was drained in all cases of perforated appendix. In Series B the practice was not uniform: six cases of abscess resolved under conservative treatment, in the remaining 126 cases with perforated appendix the peritoneum was drained in 75, the wound alone was drained in 32, and in 19 the wound was closed without drainage.

The results of peritoneal drainage, wound drainage and non-drainage may be estimated by comparing the incidence of wound infection and residual intraperitoneal abscess in the two series. "Wound infection" is taken to include all cases where healing was delayed by prolonged discharge, abscess formation or disruption of the wound. The use of chemotherapeutic drugs in 92 per cent of cases of perforated appendix in Series B complicates the interpretation of the results. In addition, the total figures are dependent upon the accuracy of the case notes: the number of wound infections recorded is probably too small, particularly in respect of Series A in which the notes are less detailed than in Series B.

The incidence of wound infection in cases of perforated appendicitis was smaller in Series B than in Series A (Table V).

In Series B peritoneal drainage and wound drainage gave the same proportion of infected wounds but the incidence of delay in wound-healing was higher when the wound was closed without any drainage.

The wound was left open after suture of the peritoneum in 28 cases in Series A and in 18 in Series B. Secondary closure of these wounds was followed by uninterrupted healing in 10 (36 per cent) in Series A and in 14 (78 per cent) in Series B. The higher proportion of successful delayed sutures in Series B is doubtless ascribable largely to chemotherapy (all these patients received antibiotics and some also sulphonamides) but the outcome may have been influenced also by the omission of drainage of the peritoneal cavity in most of the cases in the later series.

There is no important difference in the numbers of residual intraperitoneal abscesses in the two series, there being nine in Series A and seven in Series B. In the latter series there were 126 cases of

perforated appendicitis treated by operation, in the 75 cases with intraperitoneal drainage there were three cases of residual abscess, in the 51 cases in which the peritoneal cavity was not drained there

TABLE V

Drainage of Wounds and Incidence of Wound Infection in Cases of Perforated Appendicitis

SERIES A 1930-31 143 Cases of Perforated Appendicitis				
	Number of Cases	Per cent of Total	Number with Wound Infection	Per cent.
Peritoneal cavity drained	143	100	66	46.2
SERIES B 1948-50 126 * Cases of Perforated Appendicitis				
	Number of Cases	Per cent of Total	Number with Wound Infection	Per cent
Peritoneal cavity drained	75	59.5	26	
Wound drained	32	25.4	11	
No drainage	19	15.1	8	
Total	126 *	100.0	45	35.7

* Excludes 6 cases of appendix abscess treated conservatively

were four cases of residual abscess. All the cases of residual abscess in Series B occurred in patients who had received penicillin in full doses in the immediate post-operative period.

Chemotherapy—In Series B, 43.2 per cent of all cases were given chemotherapeutic drugs. Analysis of the numbers and dosage in each type of appendicitis is given in Table VI. Of the patients receiving

TABLE VI

SERIES B 1945-50

Number of Cases Receiving Chemotherapy and Average Dose in Each Type of Appendicitis

Type of Appendicitis	Number of Cases	Number Receiving Chemotherapy	Per cent of Total	Penicillin Average Total Dose mega	Sulpha Average Total Dose g	Streptomycin Average Total Dose g
Simple acute Perforated—	403	117	29.0	2.6	32.0	3.9
Local peritonitis	76	58	76.3	4.2	16.0	4.0
General peritonitis	35	35	100.0	6.2	25.0	9.2
Abscess	21	21	100.0	4.0	30.0	14.0
All cases	535	231	43.2	4.3	25.8	7.8

chemotherapy, 95.6 per cent were given penicillin alone or penicillin with sulpha drugs. Streptomycin was given to 14 patients, alone

in nine, with penicillin in four and with penicillin and aureomycin in one

In 23 cases penicillin or sulphonamide powder was dusted into the wound or peritoneal cavity

In perforated appendicitis the usual dose of penicillin was 100,000 units four-hourly for eight days

Intravenous Infusions—The notable changes in the use of intravenous infusions in Series B as compared with Series A are —

(1) Infusions were given more frequently in the later period, seven patients in Series A and 33 in Series B received intravenous infusions. All these patients had perforation of the appendix except two with simple acute appendicitis in Series B who received intravenous therapy to treat specific complications (mechanical obstruction and ileus associated with pregnancy)

(2) Infusions were given earlier in the later period, in Series A 2 out of 7, and in Series B 26 out of 33, received intravenous infusions in the immediate post-operative period

(3) Blood was used more liberally in the later period, it was given to 3 cases in Series A and to 20 in Series B. In the former, one pint was given to each of 3 patients on the second, fourth and twenty-ninth days respectively. In the first two instances it was given to combat a deterioration in condition following drainage of a pelvic abscess, and in the third it was given to a patient with empyema which developed after appendicectomy for general peritonitis

In Series B, of the 20 patients who received blood, 16 (11 general peritonitis, 2 local peritonitis, 3 abscess) were given the blood immediately after operation. Eight were given one pint and eight two pints. Of the remaining 4 cases, one was given blood for secondary hæmorrhage, one for mechanical obstruction and two for ileus

(4) Subcutaneous and rectal administration of fluid was not employed in Series B, in Series A, subcutaneous and rectal infusions were given to 8 and 2 patients respectively, in addition to the 7 patients who received intravenous infusions

Gastric and Intestinal Aspiration—Post-operative gastric or intestinal aspiration was not employed in Series A. In Series B, gastric aspiration was employed in 13 cases, and in one case intestinal suction with a Miller-Abbott tube was used successfully to treat mechanical obstruction due to pelvic abscess developing on the seventh day after removal of a perforated appendix with local peritonitis

Post-operative gastric aspiration was instituted in 7 of the 13 cases (6 general peritonitis, one regional ileitis with associated acute appendicitis) as a prophylactic measure in anticipation of paralytic ileus. Six of these patients made an uneventful recovery, one died and was found at autopsy to have a carcinoma of the tail of the pancreas with extensive metastases in the liver. Six patients had gastric aspiration as part of the treatment of complications (two mechanical obstruction, four ileus) and of these two died, both from paralytic ileus

In all but two of the 14 cases intravenous therapy was combined with gastric aspiration

Treatment of Abscess — There were 19 cases of abscess in Series A and of these five died, out of 21 in Series B there were no deaths

Sixteen of the 19 cases of abscess in Series A were treated by operation on the day of admission. The peritoneum was drained in each case. In 3 cases appendicectomy was also performed, it is notable that in two of these there was technical difficulty in removing the appendix and that both these patients subsequently died of complications. In 3 patients operation was delayed owing to doubt about the diagnosis until the fourth, eighth and tenth days respectively. Two of these patients died. The fifth death was due to inhalation of vomitus during anæsthesia.

Of the 21 cases of abscess in Series B, 13 were treated by operation on the day of admission and 8 were treated conservatively. Of the 13 treated by immediate operation, one had the abscess drained per rectum and the others were drained through abdominal incisions made over the mass. In 7 cases the appendix was removed at the time of drainage.

In two of the 8 cases treated conservatively, the abscesses failed to resolve and were later drained on the sixth and tenth days respectively after admission. In the remaining six the abscess resolved and the patients were discharged from hospital to return later for interval appendicectomy.

Anæsthesia — Comparison between the anæsthetic agents used in the two series shows that, in general, ether and chloroform have given place to pentothal and cyclopropane. There has undoubtedly been a greatly improved standard of anæsthesia which has made the surgeon's task easier. Respiratory complications have been slightly reduced. In Series A one patient died under anæsthesia, this death was attributed to inspiration of vomitus in a case of ileus, failure to aspirate the stomach pre-operatively was an important contributory factor.

LENGTH OF STAY IN HOSPITAL

The average length of stay in hospital for all cases has been reduced from 20.3 to 13.8 days. The reduction is greatest in cases of perforated appendix with local peritonitis and in those with abscess, but it is also materially reduced in simple acute and general peritonitis cases (Table VII).

This cannot be attributed wholly to improved methods of treatment. The number of beds in convalescent homes has been greatly increased since 1931 and many more patients who would otherwise have remained in the Royal Infirmary were transferred for convalescence before being sent home. None the less, the shorter stay in hospital is also related to a reduced number of post-operative complications in Series B.

COMPLICATIONS

Wound infection and residual intraperitoneal abscess have already been discussed in relation to drainage of perforated appendices

Respiratory complications more severe than mild bronchitis occurred in 25 patients in Series A and in 14 in Series B. The figures are too

TABLE VII
Length of Stay in Hospital

Type of Appendicitis	SERIES A 1930 31 Days Average	SERIES B 1948 50 Days Average
Simple acute	11.9	7.7
Perforated—		
Local peritonitis	20.2	12.4
General peritonitis	21.8	15.7
Abscess	27.3	19.3
All cases	20.3	13.8

small to be significant and the limitations of the available records must be emphasised. Nevertheless, respiratory complications did not have an important bearing on the mortality in either series. Of the deaths directly attributable to pulmonary conditions, there were in Series A one fatal case of bronchopneumonia and one case of terminal empyema, in Series B, one patient, admitted with severe bilateral pulmonary tuberculosis, died from the pulmonary infection on the sixteenth post-operative day.

There were no fatal cases of pulmonary embolus. In Series A two cases are recorded in which sudden pain in the chest occurred with fever and a friction rub. pulmonary embolus was not confirmed. In Series B, 6 cases received anticoagulants, all these had pain and swelling in the calf and in two there were also mild pulmonary signs.

Paralytic ileus developed in 19 patients in Series A and of these 16 died, in Series B, 5 patients had established ileus and of these 2 died. Thus the incidence and mortality of this complication have been materially reduced. Of the 16 patients in Series A who died with ileus 11 had uncontrolled peritonitis, but in 5 the ileus was not associated with severe peritonitis and appeared to be the principal cause of death. In Series B both the fatal cases had ileus without severe peritonitis. The treatment of ileus in Series A consisted of pituitrin, purgatives and repeated enemata. Enterostomy was performed in 7 patients and all died. Nine received intravenous, subcutaneous or rectal salines, but the infusions were small in amount and haphazard in their administration. In Series B ileus was treated by gastric aspiration and intravenous infusions together with the chemotherapy which had been given to all these patients from the immediate post-operative period.

DISCUSSION

The recent reduction in mortality and morbidity in acute appendicitis is confirmed in this series

The factor of earlier diagnosis and treatment in hospital has been stressed by other writers, particularly in the United States of America Slattery *et al* (1950) found that a greater number of patients were presenting themselves in the early stage of the disease Darling and McIver (1950) and Tashiro and Zinniger (1946) also lay emphasis on this factor In our series it appears, as has been noted, that there has been less delay in referring to hospital patients with peritonitis, but that there is still room for improvement is evident from the fact that the proportion of patients with peritonitis is not much less in the later series It is significant that in Series B all the deaths occurred in patients in whom the appendix had perforated before operation The importance of early diagnosis and early treatment is thus again emphasised

There are, however, a proportion of patients who are found to have general peritonitis when admitted on the first day of illness In Moloney's series (1950) the figure was 5 per cent In this series the figures are somewhat lower 1.7 per cent in Series A and 2.6 per cent in Series B

The importance of catharsis in producing perforation is widely held (Nuttall, 1947) On the other hand, Brown (1951) suggested that perforation is in part attributable to the delay involved in waiting to see the effect of purgation and not to the purgation itself In this series, the higher incidence of perforation in patients who were recorded as having taken purgatives confirms the belief that avoidance of purgation in doubtful cases of appendicitis would reduce the numbers of perforated appendices

With regard to operating technique, the main point of interest lies in the question of changing practice in drainage, particularly the omission of peritoneal drainage in some cases of perforated appendix in the later series It is unfortunate that no definite conclusion about the effect of omitting peritoneal drainage can be drawn from our results Among the patients with peritonitis receiving chemotherapy the incidence of residual abscess has been slightly higher in those in whom the peritoneum was not drained

The practice of leaving the wound widely open, as advocated by Wilkie (1931), has given good results in Series B The choice of this technique was probably determined partly by the views of the surgeon, but was confined to cases where the infective contamination of the wound layers occurred It appears that in these circumstances a closed peritoneum and an open wound with the help of chemotherapy give a good prospect of rapid healing after delayed closure

Comparison of the two series in respect of the incidence of residual intraperitoneal abscess shows that there has been no significant reduction

of this complication While this is at first sight disappointing in view of the benefits expected from chemotherapy, it is doubtless explained by the fact that some of the patients whose lives have been saved by chemotherapy have in the course of recovery developed a "localisation abscess"

The reduced incidence and mortality of persistent ileus in the later series is one of the striking features of the comparison The reduced incidence must be attributed largely to chemotherapy, though the use of intravenous fluids and gastric suction may have contributed to the reduction in mortality One of the recent patients with severe ileus appeared to benefit from the administration of potassium intravenously, perhaps growing appreciation of the dangers of potassium deficiency will lead to further improvement in the results of treatment of ileus

The importance of restoration of depleted blood volume in cases of general peritonitis has been emphasised by Theron and Wilson (1949) In Series B, one to two pints of blood were given to each of 16 cases of general peritonitis in the immediate post-operative period, and clinical impressions from this small number of cases suggest that blood transfusion in the early stage of the post-operative period is of great value

In the treatment of abscess, there is no evidence for or against the value of expectant treatment The influence of chemotherapy in controlling infection is again the one single important factor which distinguishes the treatment in the two series, and to it the credit must be given for the striking reduction of mortality in cases of appendix abscess

Some satisfaction that the mortality of acute appendicitis has been materially reduced in the last twenty years is fully justified, but there is no excuse for complacency It is evident that further reduction of the morbidity and mortality should be obtainable by earlier diagnosis, avoidance of purgation, improvements in the control of fluid and electrolyte balance, and the perfection of operating technique That the advent of sulphonamides and the antibiotics has been a great help in the treatment of the condition should be no more than a challenge to use these drugs, and their successors, more effectively

There has been a tendency in the past to employ the antibiotics rather indiscriminately The prophylactic administration of chemotherapy in cases of simple acute appendicitis, for example, is probably undesirable In Series B of our cases 117 patients with simple appendicitis received penicillin or sulphonamides, and in only 18 of these were the drugs given to treat specific complications In at least one case an unexplained post-operative fever abated only after penicillin was stopped Pulaski (1948) has expressed concern about the injudicious use of antibiotics and states, "There is a general tendency to institute chemotherapy or antibiotic therapy without regard to the fundamental principle of surgical management"

On the other hand, when infection has passed through the appendix

wall to involve the peritoneum, chemotherapy should be immediate and adequate. The difficulty arises that this treatment must be started before infecting organisms have been identified and their sensitivities determined. Theoretically penicillin is not ideal because many of the organisms are relatively insensitive to it, but clinical experience (such as the series we have reported) and experimental evidence (Fauley *et al*, 1944) leave no doubt that it is of value.

In bacteriological cultures from 65 of the cases with peritonitis in our series, 50 per cent of the organisms identified were *Escherichia coli* and 25 per cent were streptococci about half of which were enterococci. Thus over 60 per cent of the organisms were relatively insensitive to penicillin. It has been suggested by Crile (1946) and other workers that although *E. coli* organisms predominate in mixed peritoneal infections the chief offenders are the gram-positive cocci. It may be presumed that the value of penicillin depends mainly on its effect on bacteria which are fully sensitive to the drug. None the less, higher concentrations of penicillin are likely to bring increasing numbers of the relatively insensitive organisms under control, and when penicillin is used in these cases it should be given in large doses.

Streptomycin was used in a few of our cases, usually in combination with penicillin, while the clinical impression was favourable the numbers are too small to provide evidence. Work by Bloemers and Kempf (1950) has suggested that penicillin and streptomycin used together may have additive effect in controlling experimental *E. coli* peritoneal infections in mice. It seems probable that streptomycin should at present be employed along with penicillin in the immediate treatment of cases with peritonitis. When the sensitivities of the infecting organisms have been determined the treatment can be altered if necessary. The tendency for organisms to become resistant to streptomycin is well known, the initial dose should be adequate to eliminate any sensitive organisms rapidly and it is probably useless to continue streptomycin therapy for more than two or three days. It has been our practice to give a first injection of 1 g of streptomycin followed by $\frac{1}{2}$ g every eight hours, but even larger doses for a short period might be profitable.

Antibiotics which are to be used in the immediate post-operative period to treat perforated appendicitis must be given parenterally and the newer drugs (chloramphenicol, aureomycin, terramycin) have the disadvantage that their administration by injection must be intravenous. Their other advantages may, however, be shown to outweigh this consideration and controlled studies of their effects will be desirable when the preparations for injection become generally available in this country. Some reports are already available from America. Wright *et al* (1951), in a review of 235 consecutive cases of peritonitis, consider that aureomycin is the antibiotic of choice. Pulaski and Shaeffer (1951) consider that streptomycin and penicillin used together, and terramycin or aureomycin used singly, are effective agents.

SUMMARY

One thousand and seventy cases of acute appendicitis are reviewed with comparison of results in the periods 1930-31 and 1948-50. The overall mortality has fallen from 4.9 per cent to 1.1 per cent. The factors responsible for this improvement are considered.

It is concluded that further reduction of morbidity and mortality should be obtained by earlier diagnosis, avoidance of purgation, improvements in the control of fluid and electrolyte balance, the perfection of operating technique and progress in antibiotic therapy.

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THE EOSINOPHILE CELLS OF THE BLOOD

A GENERAL REVIEW *

By R D T CAPE, B Sc, M B, Ch B, M R C P (Ed)†

SINCE the advent of the adrenocortical hormones interest has been considerably revitalised in the eosinophile cells of the blood. It seems an opportune moment, therefore, to review the present state of our knowledge of these cells and to consider briefly the way in which ACTH and Cortisone are helping to clarify their function and their fate.

ORIGIN AND MORPHOLOGY

While it is considered by some that the eosinophils may be developed in the tissues the general consensus of opinion is that they originate in the bone marrow (Samter, 1949). One notable exception is Duran-Jorda (1943). On the basis of extremely detailed histological studies he has advanced the hypothesis that the eosinophile polymorphs are the carriers of preformed red corpuscles from the gastric and intestinal mucosæ to hæmopoietic organs. He suggests a cyclical process in which lymphocytes develop through the stage of Paneth cells in the bowel mucosæ to become eosinophils, and that the granules of eosinophils are preformed red cells which are finally extruded from the parent cell, which becomes once more a lymphocyte. His studies are intriguing but so far remain completely unconfirmed, and one must therefore regard them with considerable reserve.

The more orthodox view states that eosinophils develop from myeloblasts, passing through the intermediate stages of promyelocyte, myelocyte and metamyelocyte, in which the eosinophile granules make their appearance. The eosinophile metamyelocyte becomes a staff and then a mature eosinophil and, in common with other members of the granular series, these more mature forms are the most numerous in the bone marrow. Thus there is always a good potential supply of the cells immediately available in case of need.

Eosinophile cells are described morphologically as having a diameter of 10-12 microns. Their cytoplasm is filled by large, round or oval, pink-staining granules. The cells are actively amœboid but move more slowly than neutrophils. According to Osgood (1937) their duration of life is eight to twelve days compared with two to four days in the case of neutrophils. The fate of the eosinophils is not specifically known, but polymorphs are reported as becoming senile and dying in the blood stream, some are excreted in the saliva while most are probably destroyed in the reticulo-endothelial system.

* This paper was presented at a Seminar of the Metabolic Unit, The Vancouver General Hospital, Vancouver, B C

† R D T Cape, Fellow in Clinical Investigation, Metabolic Unit, The Vancouver General Hospital, Vancouver, B C

CONTROL OF PRODUCTION AND RELEASE

The regulation of production and release of leucocytes from the bone marrow is under the influence of four factors. These are, firstly, chemotaxis, secondly, a leucocytosis promoting factor, thirdly, the spleen and fourthly, the endocrine system.

Whitby and Britton (1947) suggest that the stimulus for the production of leucocytes varies with the type of cell, but is in all cases largely chemotactic. Thus an injection of nucleic acid or its salts will artificially stimulate a leucocytosis, a similar stimulus being provided under pathological conditions by infection with pyogenic cocci where the nuclein products of tissue destruction act as a definite stimulus. In health the stimulus, they suggest, may be supplied by the nucleoprotein set free when senile polymorphs themselves break up and disintegrate. Menkin (1938), Duthie and Chain (1939) and more recently Collumbe and Rydon (1946) have demonstrated that there is a substance, leucotaxine, which is produced at the site of inflammation and, acting by chemotaxis, draws leucocytes rapidly to the affected region. Collumbe and Rydon (1946) showed that this substance, which may be a polypeptide containing tryptophane, was present in the fluid obtained from vesicles caused by mustard gas burns, in lung oedema fluid produced by phosgene and also, *in vitro*, by the action of pepsin and trypsin on blood fibrin and blood albumin. One interesting observation was that the activity of this leucotaxine was destroyed by incubation with normal plasma or serum, but not incubation with serum from an animal in which a state of "shock" had been produced.

Menkin (1943) also described a leucocytosis-promoting factor, a pseudo-globulin which, on intravenous injection, causes an increase in circulating leucocytes averaging 200 per cent, and hyperplasia of the bone marrow. It has been obtained from turpentine effusions in dogs, and inflammatory serous effusions in man. Normal serum yields none, but it can be demonstrated in the blood of animals suffering from an inflammatory process.

The role of the spleen is complex. The effect of splenectomy on the white cells appears to be well established. There is the usual post-operative rise in polymorphs, but this rise is greater after splenectomy than after any other operation and usually persists for some weeks. Lymphocytes and monocytes appear to be particularly increased. After some weeks eosinophils are often particularly increased and may comprise 10 to 12 per cent of the differential count. This eosinophilia may last for a year or more. The effects of splenectomy on a large number of albino rats has been described by Palmer *et al* (1951). Following the operation the total leucocyte count increased approximately 100 per cent in seven days, and remained significantly elevated for seventy to ninety days, after which time there was a return to normal levels, the increase being in both neutro-

phile and mononuclear cells. Removal of as much as 75 per cent of the spleen resulted in a leucocyte increase resembling in magnitude and duration only that of control operations. When small portions of spleen were transplanted to other sites the response also resembled that which followed control operations. If splenectomy was performed in one partner of parabiotic rats no rise occurred in the leucocyte count of either animal, but if both spleens were removed a persistent rise did take place. When rats were made leucopenic by pteroyl-glutamic acid deficiency no rise occurred following splenectomy. The authors claim that their results suggest a hormonal action of the spleen on the circulating leucocytes, which acts by controlling the rate of production and liberation of the cells from the bone marrow, although their results were not entirely conclusive. There is general agreement that under certain conditions the spleen may destroy white cells but these authors' work suggests that this may not be its only role.

The influence of endocrine factors on bone marrow is varied. Thyroxine has been reported to stimulate it, particularly the myeloid series, but this is thought to be due only to its general stimulation of metabolism increasing the needs of the tissues for oxygen, to which the marrow responds. Adrenalectomized rats are reported to develop a moderate hypochronic anaemia by Piliero *et al* (1950), who also point out that there is a rise in the percentages of the myeloid components including blast cells, eosinophils and young and mature neutrophilic elements. Despite these marrow changes, however, no consistent trends were noted in the peripheral white cell picture with chronic adrenal insufficiency. Quittner *et al* (1951) gave a massive single dose of Cortisone to male albino mice and a pronounced increase in myeloid erythroid ratio occurred in the marrow. They thought that this change was due to an absolute increase of myeloid cells with a resultant increase in total cellularity. The percentage of eosinophile cells in the marrow did not change. They noted also a striking eosinopenia and lymphocytopenia in the blood and suggested a concept of blocking of the bone marrow as being responsible, or partly responsible, for this.

Our knowledge of the functions of eosinophils until recently has been no more than speculative. The most satisfactory way of considering it is to examine first the information available before the advent of the adreno-cortical hormones and then discuss what new light their advent has created. This information can also be arbitrarily and similarly divided by considering first the various conditions which give rise to an eosinophilia, as on them the pre-corticoid knowledge was largely based, while the second information is intimately connected with eosinopenia.

CAUSES OF EOSINOPHILIA

The normal level of eosinophils is 100 to 400 per cmm being approximately 1 to 4 per cent of the total white cells. Differentials

of 5 per cent or over are usually accepted as an eosinophilia. The conditions which give rise to eosinophilia are numerous and varied, and there are many conditions which may, on occasions, give rise to an eosinophilia, but do not do so consistently. These various conditions may be grouped as follows —

(1) Parasitic infestations — these commonly and fairly consistently give rise to an eosinophilia which varies in degree but is usually around 20 per cent, examples being infestation with intestinal helminths of various kinds, cysticercosis, bilharzia, filariasis and others.

(2) Allergic conditions — this is a large group including asthma, food sensitivity, hay fever, urticaria and other allergic states. The count may be as high as 10 to 60 per cent. In addition anti-bacterial immunisation is believed always to be associated with some degree of eosinophilia, and it has been suggested that if the cells disappear from the blood between injections, treatment should be suspended until their return. In the tuberculin reaction, and injections of foreign protein a tissue eosinophilia may be found at the site of injection, and in angioneurotic oedema the rise in eosinophile cells may be pronounced.

(3) Skin diseases — any infective or irritative condition of the skin may give rise to eosinophilia, for example, pemphigus, dermatitis herpetiformis, scabies, psoriasis, eczema, and prurigo. It has been suggested that the element of a foreign protein may be present in such conditions owing to the breakdown of the epidermis and the absorption of the breakdown products.

(4) Acute infections — in the acute stage of scarlet fever and rheumatic fever, especially associated with chorea, an eosinophilia of up to 10 per cent has been reported. There is, however, an equally strong, if not stronger view, that this occurs only in the convalescent stage. Friedman and Holtz (1935) have suggested that the progress and prognosis of rheumatic fever might be assessed by repeated eosinophile counts, a lack of eosinophils being noted in the acute phases, with or without an active cardiac condition, while a post-infection eosinophilia may develop during recovery. A prolonged period of eosinophile lack indicated intense severity of the disease, while continuous eosinophilia indicated convalescence. This response is characteristic of the behaviour of the eosinophile cells in any uncomplicated acute infection.

(5) Drugs — pilocarpine, phosphorus, camphor, copper sulphate, mercury, arsenic, acetanilide, sodium salicylate, and digitalis are all reputed to cause eosinophilia on occasion. Nirvanol, a barbituric acid derivative formerly used in the treatment of chorea, may cause a drug eruption with fever and pronounced eosinophilia.

(6) Finally, the other conditions which may show eosinophilia at times, but do not do so constantly, include periarteritis nodosa, a case of which Stong reported in 1928 with an eosinophilia of 79 per cent, Hodgkin's disease in which there are frequently quite a number of

eosinophile cells in the affected glands and occasionally in the peripheral blood, malignant disease, ulcerative colitis, some cases of Addison's disease and X-ray or radium treatment

Eosinophils may be found also in large numbers in hæmorrhagic pleural fluid, intestinal blood and mucous from cases of bacillary dysentery, the sputum of asthmatics, and nasal secretions of cases of vasomotor rhinitis

There are four conditions, all of them rare, in which there is a particularly marked eosinophilia. These are (1) eosinophilic leucæmia, (2) eosinophilic granuloma of bone, (3) Loeffler's Syndrome and (4) tropical eosinophilia

In eosinophilic leukemia, which is almost invariably associated with a palpable spleen, leucocytes are commonly from 20,000 to 80,000 and may be as high as 250,000. The predominant cell is a mature eosinophil. Whitby and Hynes (1936) report that the cells are unusually motile. The granules vary in size and are usually much larger than in normal eosinophils. Often they do not fill the cell, and in a Leishman stained film there may be large unstained spaces giving the appearance of vacuoles (Whitby and Britton, 1947). Their phagocytic power has been tested and found to be one-third as active against *staphylococcus aureus* as polymorphs. Eosinophile myelocytes are present only in small numbers, the average being from 0.5 to 2 per cent with a maximum of 5 per cent. Other cells are present in normal absolute numbers. The disease runs a chronic course and the average expectation of life is about six years. A few very acute cases have been reported where death has occurred in as short a period as three days (Stephens, 1935, Hay and Evans, 1929). Splenectomy does no good. Drennan and Biggart (1930) succeeded in producing a temporary drop in the eosinophile count from 23,000 to 7900 by three injections of a splenic extract but the count later rose to 49,000 prior to death.

Eosinophilic granuloma of bone is a condition affecting mainly children and adolescents. The lesions may take the form of single or multiple foci in bones, each consisting of sheets of large histiocytic cells among which are more or less conspicuous numbers of eosinophile cells, particularly eosinophile leucocytes. There are also areas of necrosis present around which actively phagocytic multinuclear giant cells are present. Jaffe and Lichtenstein in 1944 suggested that the lesions may heal by resolution. They point out that in multiple cases most of the lesions are silent and suggest that many "single focus" cases may never be seen at all. The X-ray appearances are not distinctive and may be confused with those of primary cancer. In the multiple cases the appearances on X-ray resemble those found in multiple myeloma, Ewing's tumour or secondary carcinomatous metastases. The appearances in the skull may simulate Hand Schuller-Christian Disease. These authors share the view of others (Gross and Jacob, 1942, Mallory, 1942) that this condition, Hand Schuller-Christian Disease and Letterer-Siwe Disease constitute different clinical

expressions of the same basic disorder, which seems to have a predilection for the hæmopoietic system. Its lesions apparently represent a peculiar inflammatory reaction to some as yet unknown infectious agent and are characterised cytologically at their outset by the presence in them of large numbers of histiocytes.

Loeffler's Syndrome and tropical eosinophilia have several features in common and can be considered together. The main characteristics of each are tabulated in Table I, which is based largely on data given by Apley and Grant (1944) and Weingarten (1943). The view of the former authors is that there are insufficient grounds for dividing the two conditions. They quote cases between the two extremes, such as

TABLE I
Clinical Features of Loeffler's Syndrome and Tropical Eosinophilia

	Loeffler's Syndrome	Tropical Eosinophilia
RACE	European	All races
CLIMATE	Dry	Tropical and humid, e.g. Indian coastal regions
ONSET	Mild—Few symptoms	Insidious with later acute episode
COURSE	Mild—Little systemic disturbance, transient	Chronic—Night cough and asthma—Loss of weight
DEGREE OF EOSINOPHILIA	Variable and transient (up to 66 per cent)	Variable and persistent (up to 89 per cent)
SPLENOMEGALY	No	Yes—in acute episode
X RAY	Shadowing of the lungs, variable in type always resolving quickly	Disseminate mottling of both lungs in second week of illness. After acute phase changes of chronic bronchitis
PROGNOSIS	Speedy spontaneous recovery	Chronic disease unless treated with arsenic

a typical example of tropical eosinophilia in an English airman in Cairo (Parsons-Smith, 1944) and cases of Loeffler's Syndrome outside Europe with a previous history of bronchitis related to humidity (Freund and Samuelson, 1940). Their conclusion is that the association of two such findings as pulmonary infiltrations and eosinophilia is so striking that its occurrence in two completely unrelated diseases appears improbable. That there is a definite difference, however, in the response to ACTH therapy has been shown recently by Herbert, DeReis and Rose (1950), who were able to get a dramatic reduction of the eosinophilia in a case of Loeffler's syndrome, but obtained only a rather poor response with a case of tropical eosinophilia. There are no records of cases of Loeffler's syndrome treated with arsenic.

CAUSES OF EOSINOPENIA

For some time it has been realised that a variety of conditions give rise to eosinopenia, such as hæmorrhage, cold, hæmolysis, poisons, operative procedures and a wide variety of infections. Selye (1949) in his concept of the general Adaptation syndrome has included this eosinopenic effect as part of the "Alarm Reaction". Hills, Forsham

and Finch (1948) have demonstrated that ACTH and Compound F produced a decrease in the number of circulating eosinophils and have shown that the conditions which call forth this effect are all stress stimuli. Thorn and his associates (1948) have shown that the presence of an active suprarenal cortex is necessary for the eosinopenic effect to occur.

The mechanism by which the release of the corticoid substances is obtained is rather a complex one. Hume (1949) has carried out some interesting experiments on dogs, and, based on their results,

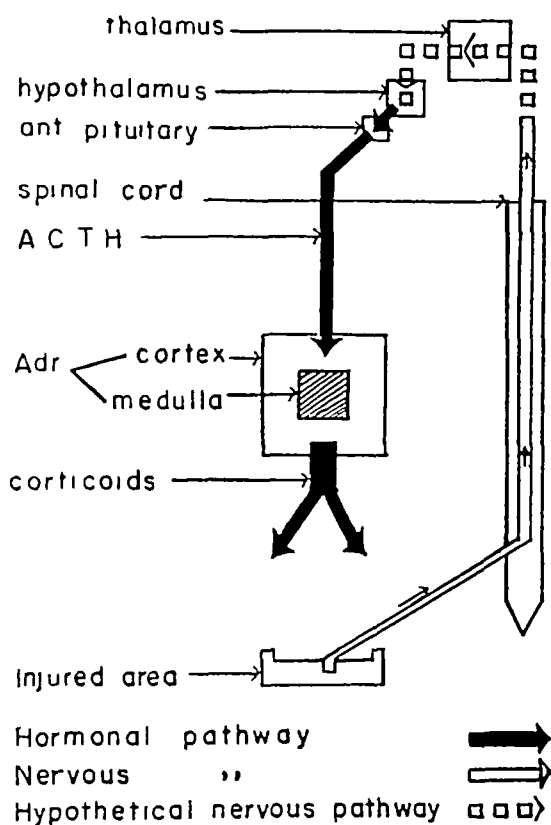


FIG 1 —Pathway of stimulus causing release of corticoids and eosinopenia (after Hume 1949)

he has suggested that three factors are necessary for the mechanism to take place. These are firstly, an intact hypothalamus, secondly, transmission of a hormonal stimulus to the anterior pituitary by the hypothalamus, and thirdly, in the case of trauma, an intact nervous connection between the injured area and brain. The mechanism which Hume envisages is shown diagrammatically in Fig 1, which is based on the results of his experiments.

Among the functions of the hypothalamus is the control of the diurnal rhythm of body temperature and sleep. Rud (1947) in a very elaborate statistical analysis of the behaviour of normal eosinophils, showed that there were significant and constant diurnal variations of eosinophile levels with a drop in the forenoon and a rise in the afternoon.

and evening. According to Godlowski (1948) sleep itself tends to speed up the recovery of normal levels of eosinophils after an eosinopenia produced in his cases by insulin shock and the consequent release of adrenalin. He and others (Eppinger and Hess, 1909) have suggested that parasympathetic stimulation, for example pilocarpine, stimulates an eosinophilia, while sympathetic stimulation produces an eosinopenia. Autonomic control is vested in the hypothalamus. Thus we see that these observations tend to confirm indirectly the concept of Hume regarding the control of the eosinopenic mechanism.

FATE OF EOSINOPHILS IN EOSINOPEMIA

What is the fate of the eosinophils when they disappear from the peripheral blood after ACTH administration? One of three things must occur, lysis of the cells, sequestration of the cells out of the blood stream into the tissues of the body, or "blocking" of the bone marrow. Godlowski (1951) has suggested that the first process occurs. He has demonstrated, in a limited series, the fact that patients or animals whose clotting mechanism has been virtually abolished by heparin do not respond to ACTH by an eosinopenia. He shows also that heparin, *per se*, will cause an eosinophilia. He concludes that "the explanation of these phenomena lie in the two apparently independent actions of heparin and eosinopenic hormones. Heparin mobilises the tissue eosinophils arrested in the lymphoid tissue during the interaction between antigen, carried by eosinophils, and specific antibodies, discharged from lymphocytes, shifting them into the circulation. Eosinopenic hormones, on the other hand, exert a direct eosinolytic action causing their disintegration in the circulating blood." Recent studies in the Metabolic Unit have shown that such an effect does not occur *in vitro* (Cape, Thomas and Palmer, 1952), an observation confirmed by other authors (Thorn, Forsham *et al*, 1951).

The question of possible sites for sequestration of eosinophils is a difficult one. The reticuloendothelial system and particularly the spleen have been suggested, but there is evidence, in animals at least, that splenectomy does not interfere with the normal eosinopenic response to epinephrine (Lucia, Leonard and Falconer, 1937). The reticuloendothelial system, however, is a very widespread and rather unapproachable one. Other sites where the eosinophils may hide out have been suggested, such as the intestine, lungs, and salivary glands.

Regarding the third possible mechanism, Durgin and Meyer (1951) have recently examined the bone marrow of mice who were given lipo-adrenal extract. There was a marked increase in the younger stages of eosinophile cells indicating an active production of new cells by the bone marrow. They point out that cells which are proliferating rapidly do not undergo much cellular differentiation and that consequently, in bone marrow thus stimulated, differentiation of

cells into mature forms and the release of mature cells into the circulating blood would not occur so rapidly as in bone marrow which did not show increased activity. They add that it is generally accepted that the granular leucocytes, as well as the lymphocytes, migrate from the blood vessels into the tissues and digestive tracts. This, they suggest, may occur more rapidly under the influence of the adrenocortical hormones, or the hormones may have some effect on the eosinophils themselves.

COMMENT ON FUNCTIONS OF EOSINOPHILS

To conclude, I would like to draw attention to one particular aspect of this problem. In acute infections the behaviour of the

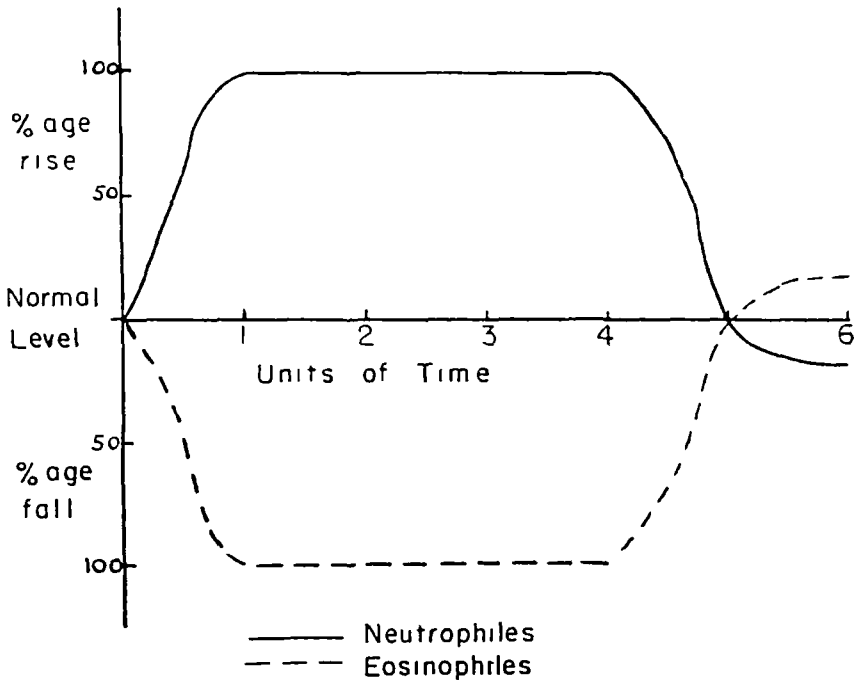


FIG 2 —Diagrammatic representation of response of granular series of white cells to acute stress (see text)

granular series of white blood cells in the majority of cases is typified in the acute phase by a polymorphic leucocytosis and an absence of eosinophils. As the process resolves and convalescence begins we find that the polymorphs return to normal, or even below normal, while the eosinophils reappear and often go on to a higher level than normal. Fig 2 illustrates very hypothetically the type of response envisaged. It seems to me that there is probably a correlation between these effects. It is reasonable to suppose that emanating from the same source and by the same mechanism the control of the granular series of leucocytes is unified. Any stress, or ACTH, I believe, produces this stereotyped response and, in the light of our present knowledge, it appears that it is mediated through the activity of the supra-renal cortex.

During the recovery period from an acute infection most patients have developed at least a temporary immunity to the organism responsible for their infection. Most of the conditions with prominent eosinophilia are considered to have an "allergic" basis. It is accepted that the main function of the white cells of the blood is a defensive one. I would suggest that the eosinophil is the second line of defence, that its function is intimately associated with the development of immunity, if I may use that word in a broad sense, and that the eosinopenia following stress is the result of a stimulus to the bone marrow which causes immediate release of polymorphs, while at the same time, and perhaps to facilitate this, withholding release of the less urgently needed eosinophils. Then, during a period of three to four hours, eosinophils in the blood before the stimulus may pass out into the tissues or digestive tract, as suggested by Durgin and Meyer (1951).

Conclusions cannot be based on speculations, however, attractive. There is a well-established link between allergic processes and eosinophilia, and Godlowski (1948*b*) has shown that the eosinophils may act as "anaphylactogenic carriers". A definite quantitative relation between the two conditions, however, is still lacking in spite of attempts to reveal it (Campbell, Drennan and Rettie, 1935). On the other hand Cortisone and ACTH have been shown to combat many allergic manifestations and appear to have an effect in immune mechanisms. Again, however, the nature of this effect remains tantalisingly obscure. Undoubtedly the future will clarify relationships between these four factors, eosinophilia and allergy, on the one hand, and eosinopenia and the adrenocortical hormones on the other, and in so doing perhaps more complete knowledge will be obtained of the functions of the eosinophil.

SUMMARY

1 The present view is that the eosinophils of the blood are formed in bone marrow and survive for between eight and twelve days in the blood.

2 The stimulus to formation and release of the cells from bone marrow is under the control of four possible factors, chemotaxis, a leucocytosis-promoting factor, the spleen and various hormones.

3 The causes of eosinophilia are outlined. The main groups of conditions considered are (a) Parasitic infestations, (b) Allergic conditions, (c) Skin diseases, (d) Acute infections, (e) Drugs, (f) Eosinophilic leukemia, eosinophilic granuloma of bone, Loeffler's Syndrome and Tropical eosinophilia.

4 The causes of eosinopenia are all essentially stress stimuli. The nature of the mechanism producing this and the nervous and humoral pathways involved are considered.

5 The fate of the eosinophils during eosinopenia is discussed, under three possibilities: (a) Destruction of the cells in the blood stream, (b) Sequestration of the cells out of the blood stream, (c) "Blocking" of the bone marrow.

6 Comment is made on the possible nature of the functions of eosinophils, and the relationship of allergy and eosinophilia on the one hand and eosinopenia and the adrenocortical hormones on the other, is noted

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BRONCHOSCOPY

MEDICAL DIAGNOSIS AND TREATMENT

By I MALCOLM FARQUHARSON, F R C S (Ed)

IT will be my endeavour in this paper to review the progress that has taken place in bronchology and to indicate its present status in diagnosis and treatment of broncho-pulmonary disease

In its early beginnings bronchoscopy was associated only with the removal of foreign bodies in the air passages. Now bronchology is a recognised specialty and bronchoscopy a proved method in the diagnosis and treatment of bronchial disease.

In addition to its diagnostic and therapeutic value, bronchology has contributed considerably to our knowledge of the physiology of the tracheo-bronchial tree. It has explained the value of peroral drainage, by ciliary wafting, tussive squeeze and bechic blast in expelling partially obstructive material before it accumulates.

Chevalier Jackson in his monumental work on this subject has explained the mechanism of obstructive emphysema and atelectasis and the interpretation of their physical signs.

In dealing with bronchial obstruction bronchoscopy has made possible many recent advances of modern anæsthesia, and the bronchoscope is now an established part of an anæsthetist's equipment.

In the management of intrathoracic disease the bronchoscopist has become a member of a diagnostic team, comprising the Physician and the Radiologist. By his ability to view the interior of the lung and to remove specimens of tissue and uncontaminated secretion, he can render invaluable aid in diagnosis.

In order to obtain the greatest assistance from such an examination the bronchoscopist must be familiar with the intricate anatomy of the bronchial tree. He must think not only of lobar bronchi and lobes but rather of segmental bronchi and broncho-pulmonary segments, so that, on viewing a bronchial orifice, he will know to what portion of lung each orifice leads, its relative size, importance and relations.

In the same way, on viewing an X-ray film he should be able to tell not only in which lobe, but also in which segment, a lesion or foreign body is lying, and he may then proceed to locate the particular bronchus leading to it.

By this method alone can our bronchoscopic reports be of greatest value to our medical and surgical colleagues.

The majority of cases are referred to us from the medical wards of the hospital, and of these cases the greatest number are those in which the radiologist has reported the presence of a doubtful shadow, suggestive of a neoplasm.

A Honyman Gillespie Lecture given on 16th November 1950

As this type of case figures so prominently in our clinic I wish to deal first with the diagnostic problems of bronchogenic carcinoma

There is general unanimity among clinicians that the only successful treatment is operative

Adrian Lambert reviewing the cases treated at the Bellevue Hospital, New York, between 1939-46—349 cases—states that 20 per cent of the cases admitted with carcinoma of the bronchus were considered suitable for operation. Seventy were explored and only 25 had a tumour which was removable, of these 7 died in hospital

Rienhoff of Johns Hopkins describes a similar experience—327 cases of which 215 were inoperable and 112 cases operable—39 per cent survived operation

Brock in this country has a similar tale to tell. One and all explain these gloomy figures as due entirely to the fact that the cases were not diagnosed early enough

In reviewing case histories of many of these patients found to be inoperable, one is struck by the fact that the correct diagnosis could have been made at a much earlier date if the significance of certain vital signs and symptoms had been appreciated and if the need for X-ray and bronchoscopy had been realised

The signs and symptoms of greatest significance are —

- (1) Persistent cough, with or without blood-stained sputum, seen in 50 per cent of the cases. Brock suggests in patients between forty and sixty it is almost diagnostic
- (2) Symptoms of respiratory infection—slowly resolving and recurring pneumonia
- (3) Henkin Triad—fever, leucocytosis, anæmia
- (4) Pain in the chest—late
- (5) Wheezing

These, however, are protean symptoms

Norris from the Chevalier Jackson Bronchoscopic Clinic has suggested that the early manifestations of a bronchial carcinoma depends to a large extent on its point of origin, so that an arbitrary classification based on location is of more practical value for clinical study

Separate consideration might be given to those tumours which arise in the main or lobar bronchus, those which arise in the segmental and those arising peripherally

It is generally held that over 50 per cent of carcinoma arise in a main or lobar bronchus, a much smaller number in one of the segmental bronchi and some 25 per cent arise peripherally

SYMPTOMS OF A CARCINOMA OF THE MAIN OR LOBAR BRONCHUS

The earliest symptom is bronchial irritation—chronic unproductive cough—this is followed by symptoms dependent upon increasing

bronchial obstruction which interferes with the air exchange and drainage. In its lesser degrees giving rise to a wheeze localisable to one or other side—the "asthmatoïd wheeze" described by Chevalier Jackson.

When the obstruction is more marked, interference with the normal bronchial drainage gives rise to secondary infection resembling one of the common lower respiratory infections—bronchitis or pneumonia.

PERIPHERAL BRONCHUS

25 %

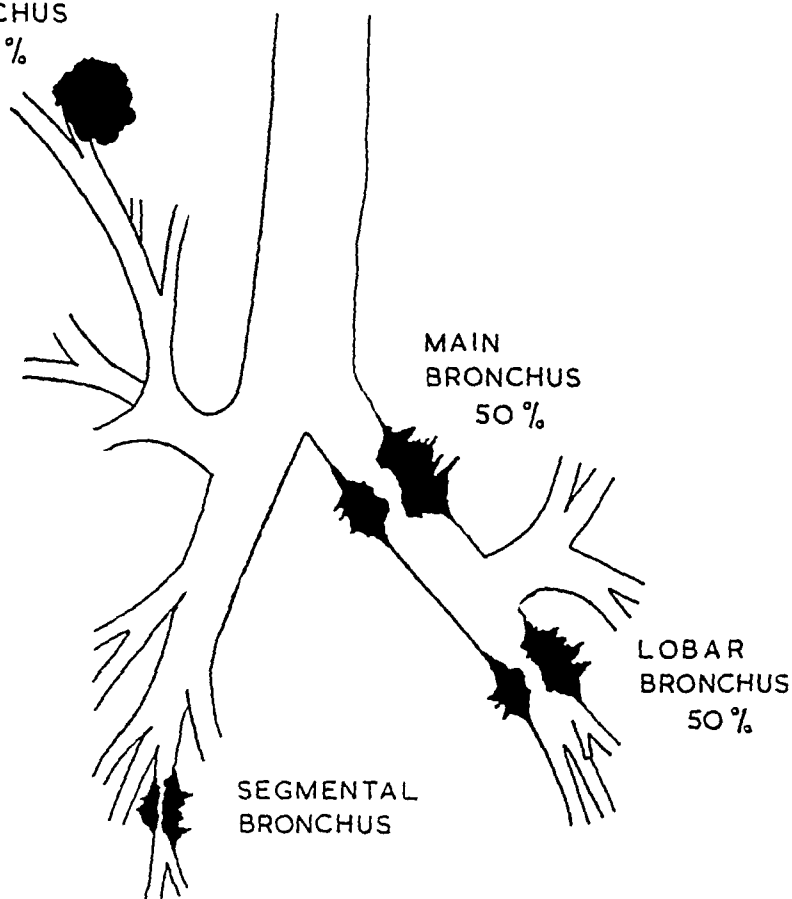


FIG 1 —*Bronchogenic carcinoma*—Arbitrary classification. Based on location. The early clinical and X-ray findings depending on the position of the tumour. (Adapted from Charles M. Norris, M.D., F.C.C.P., *Diseases of the Chest*.)

Hæmoptysis occurs early when one of the larger bronchi is involved.

At the outset, therefore, there may be no abnormal physical signs or X-ray findings. Their appearance proclaims the presence of some degree of bronchial obstruction. The existence of a tumour, therefore, is suspected because of the effect it has upon the air exchange and bronchial drainage.

The earliest physical signs will be smaller respiratory excursion

It will be realised that the only way of making a positive diagnosis of bronchogenic carcinoma prior to operation is by microscopic examination of a piece of the tumour

In reviewing the literature it is found that a diagnosis was made by biopsy in 60 to 80 per cent of cases

Louis Clerf at the Jefferson Hospital from 1930-45 recorded a positive biopsy rate of 65 per cent in 336 cases Holinger 70 per cent in 175 cases Overholt 62 per cent

The figures at the Royal Infirmary, Edinburgh, and Bangour Hospital, show a positive biopsy rate of 60 per cent

TABLE I

Radiotherapy Department, Royal Infirmary, Edinburgh
Cancer in Lung 1935-48

Showing the Number of Cases of Carcinoma of the Lung 1935-48 It is Interesting to Note there is a Considerable Increase in Numbers in More Recent Years

Number bronchosoped and histologically proven bronchoscopically	242
Number otherwise proven, i.e. by post mortem or biopsy of gland or metastatic deposit	408
Number not proven	623
Total number	<u>1273</u>

Cancer in Lung	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947	1948	Total
Bronchosoped and histological +	2	3	4	8	7	11	9	20	20	30	24	23	23	58	242
Gland or metastases + post mortem +	12	6	25	15	18	17	14	25	12	33	35	48	77	71	408
Not histologically proven	13	18	21	27	36	41	37	42	59	69	62	69	62	67	623
Total	27	27	50	50	61	69	60	87	91	132	121	140	162	196	1273

At first sight these figures may appear encouraging until they are offset by the number of cases successfully operated upon—few surgeons would claim higher than 10 to 15 per cent of the total number

It has appeared that the higher the percentage of positive bronchoscopic biopsies, the higher the percentage of inoperable cases

From this survey it is evident that in order to treat this disease successfully an earlier diagnosis must be made, before the large bronchi become obstructed, and a search made for the lesions outside the visual field of the bronchoscope—in the peripheral bronchi and upper lobe

In an endeavour to overcome these technical difficulties use has been made of the retrograde telescopic lens system for the upper lobe lesions, but this did not fulfil the hopes placed in it Pneumothorax in the upper lobe lesions was employed but did little to improve the radiological visualisation of the tumours

Aspiration biopsy has been employed to gain this end successfully but has been condemned by the thoracic surgeon because of the danger of cancer implantations down the track of the needle

In this country, Barnett, Dudgeon and Gower examined the sputum for malignant cells and claimed a high percentage of accurate results. These claims, however, have not been universally confirmed.

Since there is a constant exfoliation of cells from the free surface of a tumour, direct examination of the bronchial secretion would appear to give more hopeful results.

This method was employed by Herbut and Clerf who, seeing the excellent results obtained in carcinoma of the uterus by the Papanicolaou technique, resolved to adapt it for use in the diagnosis of carcinoma of the bronchus.

A review of their results showed that they obtained a positive cytological diagnosis in 22 out of 30 cases—73 per cent—of proved carcinoma. In this same group the histological diagnosis of carcinoma based on bronchoscopic biopsy was 36.6 per cent.

Since the introduction of the cytological study of bronchial secretion in 1946 certain changes in technique have been made.

Now in all cases an X-ray is taken to aid the localisation of the lesions to a lobar segment, lobe or lung, and then a routine bronchoscopy is performed for diagnostic purposes, secretions from the trachea and larger bronchi are discarded as marked dilution and disintegration of cells occurs. Secretions are collected in a special collector from the bronchial divisions under suspicion and are sent for pathological examination.

The introduction of a few c.c. of normal saline into the bronchus under examination, and its reaspiration after a few minutes, aids in the collection of material.

In examining the upper lobe better results are obtained by placing the patient on the affected side, after the bronchoscope has been introduced, and aspirating as before.

Louis Clerf and Herbut in 1947 carried out a follow-up study to determine the comparative value of cytological diagnosis and other accepted methods.

The total number of observed cases was 180, all known cases of carcinoma based upon bronchoscopic biopsy, exploratory thoracotomy, post mortem and cytological study.

All cases diagnosed by cytology were corroborated by one of the previously mentioned methods.

It was further noted that a proportionately larger number of bronchoscopically negative, cytologically positive, cases were amenable to surgical removal, than bronchoscopically positive cases alone. This, of course, was due to the earlier diagnosis made possible by this method, and to the fact that the situation of the growth was segmental, rather than lobar, in origin.

I should like to mention here, while discussing the cytology of bronchial secretions, the further use of this technique by Clerf and Herbut as an aid to the diagnosis of early pulmonary tuberculosis.

These workers, while studying bronchial secretions for cancer

cells, were puzzled by the presence of, in some cases, rounded clusters of ciliated epithelial cells, single ballooned and vacuolated ciliated epithelial cells, and giant cells of the Langhans type

All cases save one, in which these cells were found, gave a subsequent positive culture of tubercle bacilli some months later

The authors explain the phenomenon by suggesting that there must be a tuberculous ulcer of the epithelium of the bronchus at the level where the epithelium becomes ciliated. In the process of ulceration the cells break off in clumps, and, since they are spontaneously sloughing, their borders are rounded

This method is particularly helpful in differentiating pulmonary tuberculosis from carcinoma in atypical lesions

As yet I have no personal experience of this further application of the Papanicolaou technique

BRONCHIAL OBSTRUCTION

Bronchial obstruction may be defined as any morbid diminution of the lumen of the bronchus

Bronchial obstruction enters into every medical and surgical problem of pulmonary disease, and a knowledge of the subject is fundamental to an understanding of these diseases

It may be said that no one goes through life without encountering bronchial obstruction in one form or another

Our knowledge of this subject is due almost entirely to the pioneer work of Chevalier Jackson to whom we owe so much for an understanding of this vital subject

He has explained the physiology of the bronchial mechanism and the mechanics of bronchial obstruction. His work, more than any other, has been responsible for the saving of countless lives and the making possible of so many of the advances of surgery and anæsthesia

PHYSIOLOGICAL BASIS OF BRONCHIAL OBSTRUCTION

The cough reflex has been aptly termed the "Watch dog of the lung". Upon its vigilance rests the safety of the lower air passages, being ever ready to extrude any exogenous or endogenous intruders from the lumen of the bronchus

The normal mechanism of pulmonary drainage is dependent upon three main factors

- (1) The ciliary wafting
- (2) The tussive squeeze
- (3) Bechic blast

These three forming what has been called the mechanism of normal peroral pulmonary drainage

When the function of any of these three is interfered with some degree of bronchial obstruction will ensue

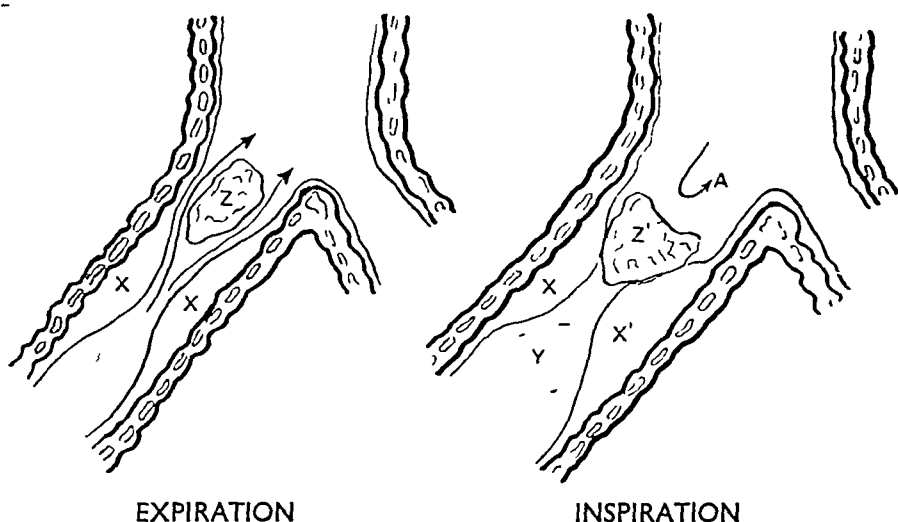


FIG 2—*Mechanism of obstructive atelectasis* produced by a mass of secretion (Z) acting like a check valve in a pump. It rests on a ridge of swollen bronchial mucous membrane at the opening of a bronchus (X). At each expiration it is lifted by the expiratory current, allowing air to escape. At the beginning of inspiration the suction pulls the mass down (Z') tightly as on a valve seat so no air can enter (A). The final result of this will be atelectasis. A mass of secretion (Y) below the inflammatory narrowing (X') would cause a pumping in of air and so emphysema. (Adapted from Jackson and Jackson, *Diseases of the Nose, Throat and Ear*)

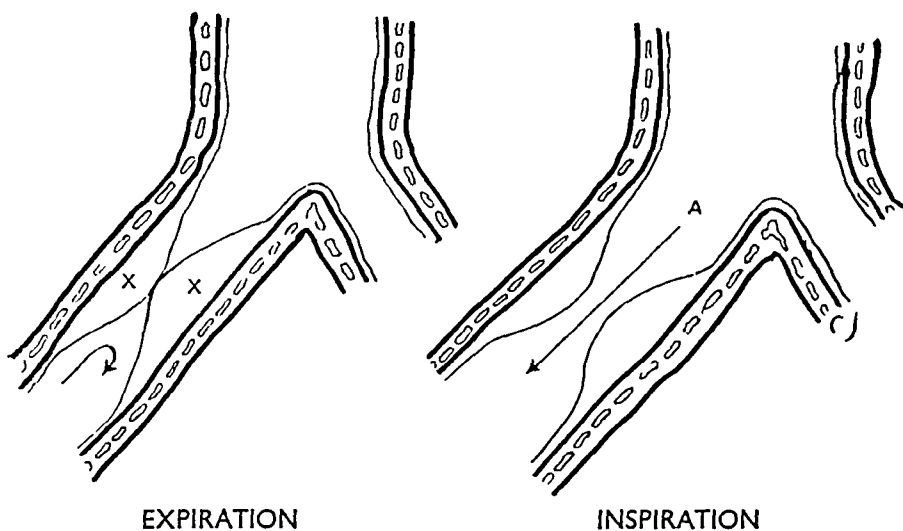


FIG 3—*Expansile check valve*—The swollen mucous membrane (A) comes in contact at the commencement of the start of the expiratory phase, the bronchial diameter is sufficient to make an opening for the admission of air (A). At the beginning of the following expiratory phase the diminution of the bronchial diameter closes the narrow lumen, trapping air below the obstruction. Obstructive emphysema will result in that tributary area. (Adapted from Jackson and Jackson, *Diseases of the Nose, Throat and Ear*)

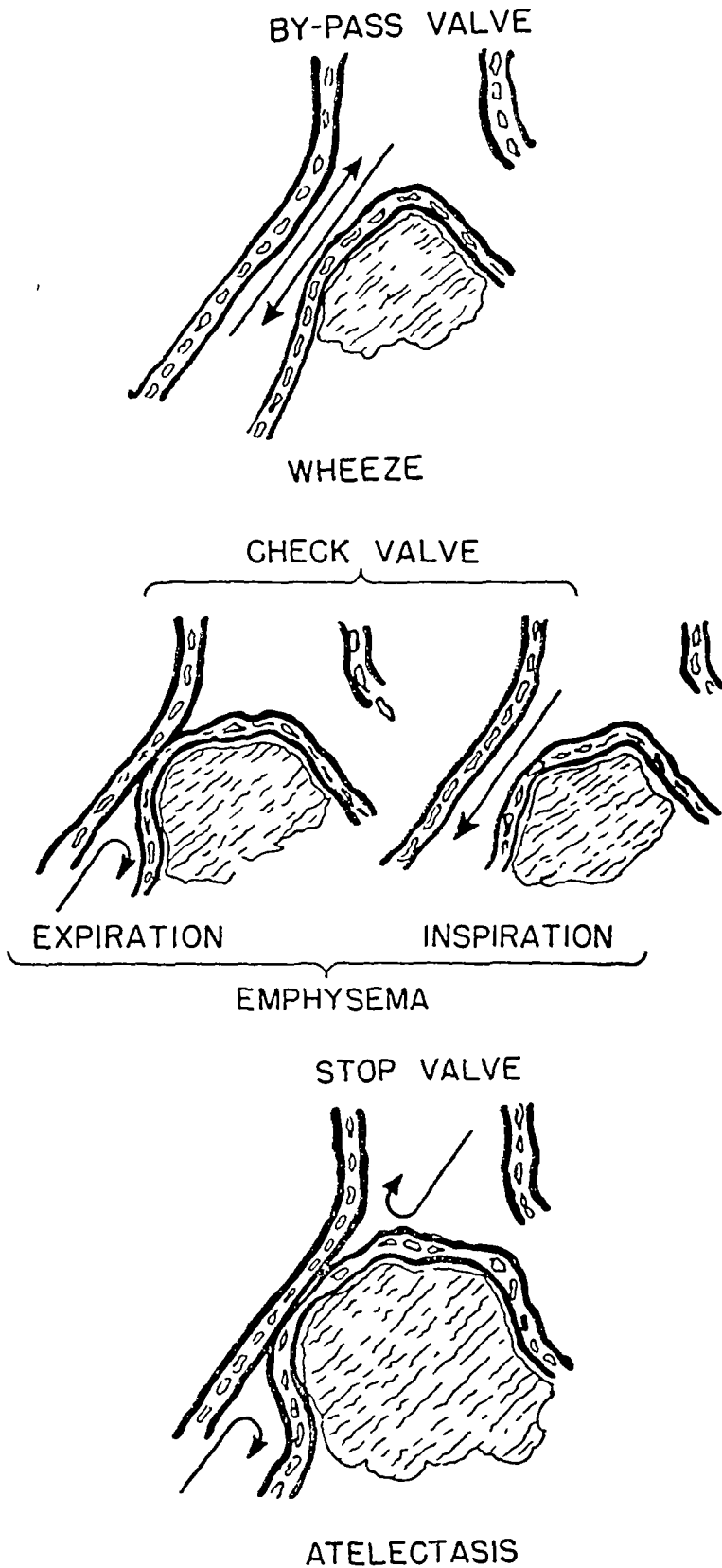


FIG 4—Showing the method whereby a peri bronchial lesion, tuberculous or malignant gland, can produce three different types of bronchial obstruction with their own physical signs (Adapted from Jackson and Jackson, *Diseases of the Nose, Throat and Ear*)

The first factor, of course, must be a diminution of the bronchial lumen

The three elements of peroral drainage may be upset by many factors, for example —

The ciliary wafting may be thrown out of action either by a clogging of the cilia by mucosal swelling or by the adhesive and cohesive nature of the bronchial secretions

The bechic blast, being the principal vehicle for removing pathological material, is dependent for its action on the pressure of air below it, so that in the event of bronchial obstruction its action is limited. In such a case it is dependent upon the tussive squeeze for supplying it with secretion for expulsion

An auxiliary agent is the movement of the tracheobronchial tree constituting a rhythmic enlargement and elongation of the lumen and a diminution and shortening of the lumen—this alternating eighteen or more times per minute

THE MECHANICS OF BRONCHIAL OBSTRUCTION

The bronchoscope may be said to have revolutionised one's conception of bronchial obstruction

Chevalier Jackson has shown how the problem is related to the science of mechanics, involving the action of forces upon bodies both solid, liquid and gaseous

Bronchoscopic examination revealed the fact that obstruction in the living is valvular in action

Valvular obstruction of the bronchus is dependent upon the normal movements within the bronchus

The different types of valvular action that may occur have been described as —

- (1) Stop-valve—arresting all flow of air
- (2) By-pass valve—allowing a limited flow of air in both directions
- (3) One way valve—allowing a flow in one direction only

The one way or check valve will permit the entrance of air into a lobe but prevent exit of air from it

This will give rise to an emphysema of the lung below

The ball-like action of these valves may be produced by a mass of secretion falling back on an annular stricture formed by œdematous mucous membrane or a tumour mass in the bronchus

In the case of a foreign body lying in a bronchus, at first air may be seen to pass down between it and the bronchial wall by a mechanism of enlargement of its lumen on inspiration, while on expiration no upward passage of air occurs. This gives rise, initially, to an emphysema of the lung below the foreign body, later reactionary swelling of the mucosa around the foreign body occurs and no

air passes in either direction Emphysema is thus followed by atelectasis

Bronchial obstruction is commonest at the extremes of life, occurring in the new born babe as an inhalation of amniotic fluid and in the aged as hypostatic engorgement and a drowning in their own secretions

The case of the young child deserves special study Here the bechic blast and tussive squeeze are weak and the diameter of the bronchi small

A swelling of the mucosa of 1 mm in an adult bronchus of 10 mm interior diameter would reduce it 36 per cent In an infant, such a swelling in a 2 mm bronchus would reduce it 100 per cent or cause complete obstruction

A realisation of these facts explains the gravity of acute bronchitis or broncho pneumonia in the young, and shows how pulmonary complications are the terminal phase of most deaths in children

Infections—acute and chronic, tuberculosis, mycotic, along with inflammatory mucosal swelling and inflammatory products are among the commonest causative factors

PRE- AND POST OPERATIVE MEDICATION

The two drugs in commonest usage for this purpose are morphine and atropine in combination These drugs exert their main action in two ways —

- (1) To reduce the normal glandular secretion and by so doing increase the cohesiveness and adhesiveness of the secretions—adhesive masses forming within the bronchus
- (2) By suppression of the cough reflex, peroral pulmonary drainage being abolished

The result is that these abnormal secretions lying stagnant within the bronchus give rise to bronchial obstruction and atelectasis

As early as 1904 Chevalier Jackson demonstrated the dangers of the indiscriminate use of these drugs—how little heed has been paid to his teaching

Pre- and post-operative medication must not be judged by rule of thumb, but individually, for each patient, taking into consideration the age, type of operation, whether post-operative bleeding may occur and involve the upper air passages or affect the upper abdomen with diaphragmatic interference

Prolonged operations with suppression of the cough reflex will favour the formation of obstructive plugs by the accumulation of pathological bronchial secretions

Failure to utilise pre- and post-operative direct laryngoscopic aspiration of these secretions is an important factor in the production of bronchial obstruction and its sequelæ which previously were termed post-operative pneumonia

The avoidance of these complications is no longer in the domain of the surgeon but of the anæsthetist, whose duty it is to maintain a clear airway to the lungs before, during, and after the operation

The importance of a correct post-operative posture cannot be overstressed, dorsal recumbency favouring the development of bilateral bronchial obstruction, especially of the posterior segments of the lung, while prolonged lying on the same side favours obstruction of the lobar and segmental bronchi of the dependent side

Treatment of bronchial obstruction is, of course, based upon the accurate diagnosis of the pathological condition by bronchoscopic examination

Foreign bodies can be removed by forceps, be they inspired or endogenous in nature

In cases of bronchial obstruction due to the presence of secretions of high viscosity these can be removed by the so-called synergistic bronchoscopic aspiration, this, in fact, means aspiration in co-operation with the tussive squeeze. The aspirator removes the secretions, each time it is expelled by the tussive squeeze, from the periphery of the lung into the larger bronchi and before it can be inspired again by the deep inspiration following a cough

In the early stages and as a prophylaxis before any of the smaller bronchi have been blocked and atelectasis occurred, the use of a gum elastic catheter passed through a laryngoscope down just short of the carina will be sufficient to clear the passages

A word of warning in the young child is necessary, to avoid ballooning the lung by the production of a positive pressure, a tube small enough to allow of the free interchange of air between the vocal cords should be chosen

Where definite signs of atelectasis or emphysema are detected bronchoscopic aspiration will be required

In cases where the obstruction is due to cicatricial stenosis the use of dilators is recommended in preference to endoscopic bronchotomy

PULMONARY ABSCESS

Until the growth of thoracic surgery, bronchoscopic aspiration was the recognised method of treatment, and many were the lives saved by this means

There can be no doubt, however, that many patients are rendered chronic invalids who might have been cured by lobectomy or external drainage

For this reason, therefore, bronchoscopic treatment has fallen into disfavour, and rightly so, in the treatment of chronic lung abscess

Bronchoscopy has a place in the treatment of acute abscess by initiating drainage and allowing the abscess to go on to spontaneous closure and healing

Even in the acute abscesses a watchful eye must be kept on the

case to see that improvement is maintained, otherwise further measures must be resorted to, to avoid serious complications ensuing

No case should be treated by bronchoscopy for more than four weeks

BRONCHIECTASIS

What has been said about the bronchoscopic treatment of lung abscess applies in a large measure to bronchiectasis

Its main value now lies as a prophylactic measure, as it can be safely said that if every patient with a slowly resolving infection of the lower respiratory tract received bronchoscopic aspiration the incidence of bronchiectasis would be greatly reduced

In the fully established case, if localised to one side, lobectomy is undoubtedly the treatment of choice

When the lesion is bilateral, or otherwise unsuitable for surgery, benefit may be derived by regular bronchoscopic aspiration of the pathological secretions lying in the bronchiectatic septic tank, thereby rendering the patient's life comfortable, as well as that of his associates

BRONCHIAL ASTHMA

This is essentially a medical problem, but the assistance of the bronchoscopist is often sought to aid in the diagnosis and treatment of the atypical type of case, when the clinical features and symptoms do not conform to what is recognised as "true asthma" and certain conditions that simulate asthma

In this kind of case all types of bronchial obstruction are found, some manifesting a wheezing sound and no dyspnoea

Bronchoscopy is indicated in all recent cases in which there is wheezy respiration, constant or paroxysmal, nocturnal or diurnal

The aphorism of Chevalier Jackson that "all is not asthma that wheezes" must ever be kept in mind

This brings to mind the patient referred recently from the Medical Wards by a very astute Resident. She was admitted unconscious with a supposed epileptiform seizure. On regaining consciousness the Resident noticed that her respirations were wheezy and that she was developing considerable dyspnoea. He considered the possibility of a foreign body and referred her for bronchoscopy

On bronchoscopy a hazel nut was removed from the right main bronchus. On questioning the patient later I found that she had been eating hazel nut chocolate before the attack came on

It should be borne in mind that typical slow expiratory respiration occurs in a variety of conditions from a vegetable foreign body in the bronchus to cancer of the lung in the adult

As regards therapy, aspiration will give dramatic relief in many cases by removing the viscid secretions and avoiding obstruction

Aspiration through the aspirating tube passed between the cords is all that is required in most cases

PULMONARY TUBERCULOSIS

Pulmonary tuberculosis was considered for many years one of the main contra-indications to bronchoscopy. Now, this is no longer so, and by many it is considered a necessary routine examination before considering collapse therapy. By so doing the presence of adhesions and bronchial obstruction can be diagnosed which would otherwise vitiate a satisfactory collapse. It would also exclude the presence of pyogenic cocci in the cavity to be collapsed, which, if undiagnosed, might lead to disaster.

Its greatest contribution, however, is in the recognition of tracheo-bronchial lesions which would also interfere materially with collapse therapy.

Treatment by silver nitrate application has proved beneficial.

From what has already been said it will be evident that the work of a bronchoscopic clinic falls into two main categories.

First—The emergency cases involving the removal of foreign bodies from the air passages, or the aspiration of abnormal secretions from the bronchi, be they cases of post-operative collapse or acute medical conditions.

For this type of case an emergency service must be provided, available at all times, to the surgical and medical wards of the hospital.

Second—The diagnostic work which forms the great bulk of the cases.

This can best be carried out in a clinic designed specially for the purpose where there will be the considerable equipment necessary for dealing with the various conditions met with in broncho-pulmonary disease. In such a clinic the services of a physician, surgeon and radiologist will be available as members of a diagnostic team.

This paper has dealt with the present status of bronchoscopy—what of the future?

The future of bronchoscopy as I see it, is linked closely with its preservation as an individual science related in the closest way to the sister sciences of laryngology and thoracic surgery, but not absorbed by them.

No paper on endoscopy would be complete without reference to the late Dr Ewart Martin whose pioneer work in the speciality will always be remembered in this country. I feel very honoured to have trained under him and to have had the privilege of including his figures among those of my own.

In conclusion, I would like to express my thanks to Drs Chevalier and C. L. Jackson and Dr Louis H. Clerf, Philadelphia, also Professor McWhirter, Edinburgh, for the help they have given me in the preparation of this paper.

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OBITUARY

JOHN PATON MCGIBBON, M D , F R C P E , D R , D P H

As a result of an accident Dr McGibbon died in Edinburgh on 21st April at the age of 48. He was the son of the late John McGibbon, sometime Professor of Midwifery at the University of St Andrews. Early in life he was the victim of a severe attack of poliomyelitis which left him weak and crippled. Later he was adversely affected by diphtheria and scarlet fever, and in recent years by chronic laryngitis and bronchiectasis, besides being subject to migraine. Such physical disabilities would have daunted most men but not McGibbon, though undoubtedly they influenced his character and career. It was thought that his feeble health would preclude him from taking up medicine, so he worked for a time in an office before he took up the study of medicine. He qualified in 1929, and acted as resident in medicine and in surgery in the Royal Infirmary and as medical officer at the City Hospital. The D P H he obtained in 1932 and later deciding to take up radiology as his specialty he obtained the D R in 1935. The membership of the Royal College he gained in 1933 and he became a fellow in 1937. After a period as assistant radiologist in the Western Infirmary, Glasgow, he returned to work in the Royal Infirmary of Edinburgh. By diligent study, logical thought and keen observation he made himself master of his subject in all its aspects, and his opinion was highly valued by those who sought his help. His special knowledge and patient study of congenital heart disease were of special value in the diagnosis and treatment of such cases.

He took a large share in the teaching in the radiological department and he was a master in the art of exposition. His skill came largely from his patience, his humour, his insistence and his ability to appreciate the difficulties of each individual student.

Despite his numerous handicaps he had the greatest interest in all forms of sport, and perhaps this was the keynote of his character. He revelled in fair play, but reacted most vigorously and fearlessly to any sign of meanness, selfishness, personal greed or aggrandisement. He was modest in achievement and had all the qualities of the sportsman: courage in adversity, endurance and perseverance despite physical burdens which would have crushed any ordinary man, and loyalty of the highest degree. He did not make friends easily but those who were lucky enough found in him a friendship of a rare excellency. His subtle sense of humour and the richness of his character made him delightful and inspiring company.

McGibbon was a shining example of the power of man to overcome the greatest difficulties, and his character and devotion to duty have been an inspiration to many. His loss will be widely felt.

ANDREW EDWIN HUNTER, M D

IN the passing of Dr A E Hunter on 1st July, Falkirk loses one of its best-loved personalities

If a living and enduring monument to his memory be necessary, surely it must be the Infirmary, for he was the genius of the place. From that tentative beginning, thirty-five years ago, when he undertook to act as visiting physician and surgeon for a trial period of some months in the old building in Thornhill Road, he has watched over its growth and rejoiced in its success. How many realise that, for almost thirty years, all the emergency surgery of the district was performed by Dr Hunter? In spite of heavy calls upon his time and energies, he never overlooked the urgent claims of his busy private practice. During these crowded years he was an inspiring teacher to nurse and doctor alike, and many will remember with pride and thankfulness his interest and encouragement.

His help as Consultant was frequently sought by his colleagues in family practice, and he was never too busy to answer these requests. His colleagues understood what it was to be strengthened by his fortitude, comforted by his wisdom, and cheered by his high-hearted happiness. His complete absorption in his duty left him little time to cultivate outside interests, yet his was a many-sided genius, and he might have made a distinguished contribution to the cultural life of the community. Only his colleagues were permitted on rare occasions to enjoy his diverse gifts, and his appearances at the Falkirk and District Medical Society were illuminated by grace and wit, choice phrase and speech above the ordinary range.

He measured his life by the Golden Rule, a deep unswerving loyalty to the ideals of his profession, without care for his own reputation or gain, and indifferent to popular acclaim or criticism so long as his own exalted conception of duty were fulfilled.

NOTE

At a meeting of the Royal College of Surgeons of Edinburgh held on 21st May 1952, Professor Walter Mercer, President, in the Chair, the following who passed the requisite examinations were admitted Fellows —Suleiman Abul-Husn, M D UNIV BEIRUT 1945, David Hobson Biggs, M B, CH B UNIV CAPE TOWN 1943, Charles Bruce Cornish, M B, CH B UNIV NEW ZEAL 1947, Ronald Patrick Cumring, M B, CH B UNIV ABERDEEN 1945, Basil Manfred de Saxe, M B, B CH UNIV WITWATERSRAND 1945, Amy Dhunjbhoy Engineer, M B, B S UNIV BOMB 1938, M D 1943, Wilfrid Grundill, M B, B CH UNIV WITWATERSRAND 1944, Rahman Habib-Ur, M B, B S UNIV PUNJAB 1946, Jeremiah Dominick Hennessy, M B, CH B NAT UNIV IREL 1945, Jagat Singh Karanwal, M B, B S UNIV LUCKNOW 1942, Alexander Marshall, M B, CH B UNIV GLASG 1945, Jitto Manoo Mehta, M S UNIV BOMB 1948, Allin Herbert Moore, M D UNIV MANITOBA 1944, Herbert Dick Rawson, M B, CH B UNIV NEW ZEAL 1947, Theodore Francis Redman, M B, CH B UNIV MANCH 1940, Alexander Ernest Rublack, M D, C M QUEEN'S UNIV ONTARIO 1945, Douglas Paviour Short, M B, CH B UNIV NEW ZEAL 1946, George Alfred Silley, M R C S ENG, L R C P LOND 1942, Leslie Simon, M B, CH B UNIV EDIN 1947, Perin Ratansha Toddywala, M B, B S UNIV BOMB 1947, M D 1949, Donald Mark Whitley, M D UNIV MANITOBA 1942

NEW BOOKS

Untoward Reactions of Cortisone and ACTH By V J DERBES and T E WEISS
Pp vii+51 Oxford Blackwell Scientific Publications 1951 Price 8s 6d net

This little book, the 131st publication in the American Lecture Series, reviews the vast literature on Cortisone and ACTH listing and describing the manifold undesirable effects which may be produced by these hormones. It contains 96 references and is a concise and efficient guide for the many who should know the dangers but have little time to cull them from the original papers. It emphasises the possibility of avoiding undesirable effects by careful attention to detail and selection of patients. The interdiction of these agents in the tuberculous (p 40) should not obscure the prime indication for the use of Cortisone in Addison's disease.

Color Atlas of Morphologic Hematology By G A DALAND, B S Edited by T H HAM, M D Pp v+74, with 14 coloured plates and 9 figures Harvard University Press London Geoffrey Cumberlege 1951 Price 32s 6d net

The author is an expert technician in hæmatology, and the editor a professor of medicine. The basis of this study is a series of films stained with Wright's stain which gives particularly beautiful results. The coloured reproduction of the blood cells has been excellently done. Each plate includes a large number of typical cells selected from slides, and shown separately so that they can be fully studied. Bone marrow cells are illustrated in so far as they may appear in the circulating blood. There is in addition a useful text, describing the features to be looked for in each disease and the significance of the various findings present. The book covers all the ordinary diseases of the blood and should be of the greatest value as an aid to the recognition of the various disorders. Considering the high standard of its production the price is very reasonable.

The Kidney Structure and Function in Health and Disease By HOMER W SMITH
Pp xxii+1049, with 153 illustrations London Oxford University Press
1951 Price 100s net

Past discussions of the function of the kidney have been largely limited by the rival theories of tubular absorption and excretion. The result of this controversy has been to focus attention on the excretory function to the exclusions of the equally important role as regulator of the blood-content, electrolytic and organic. The work of recent years has been of wider conception and has led to the establishment of the part truth contained in each of the rival theories and to the fuller understanding of the high complexity of the kidney function.

Homer Smith's *The Kidney* is rightly accepted as the leading modern textbook of renal physiology. Discarding the theoretical discussions of the past for the wider knowledge of the present time, it enters into every detail with clarity so that even the difficult complex clearances are readily understood. It is not a book for those in search of elementary physiology, it requires a full basic knowledge for appreciation of its value.

The subtitle indicates that it is a book of practical application. The clinician will value it as highly as the physiologist. Though pathology is but little dealt with, the present physiological views are ably applied to renal diseases and also to the effects of general diseases on the kidney.

A bibliography of 2300 references is indicative of the extent of the study.

Physical Medicine and Rehabilitation for the Clinician Edited by FRANK H KRUSEN, M D Pp xv+371, with 93 illustrations London W B Saunders
1951 Price 32s 6d

One of the axioms enunciated in this book is that the physician should prescribe physical methods of treatment with the same accuracy as he does potent drugs. In order to do that he must know the rationale of physiotherapy with its limitations and contra-indications. This is a textbook from which clinicians would derive considerable help and it would enable them to relieve the physiotherapists from a great deal of unnecessary work and so let them give more satisfactory treatment to those who require prolonged sessions. Study of this book would give the doctor confidence in explaining to the querulous patient whether physiotherapy would be beneficial or of no value. There are forms of treatment which the doctor or the patient can carry out efficiently if sufficiently instructed and there is no need to go beyond this book for advice on the subject. Study of this volume would repay the time spent.

Decompression Sickness Caisson Sickness, Divers' and Flyers' Bends and Related Syndromes By JOHN F FULTON, M D Pp 437, with 88 figures London W B Saunders 1951 Price 42s 6d net

Compressed air illness or caisson disease is an occupational malady suffered by men who work in increased atmospheric pressures. It is caused by the vaporisation of nitrogen from the blood as a result of too rapid or incomplete decompression. Bubbles of gas present in the blood stream or tissues give rise to joint pains—"the bends"—abdominal cramps and other symptoms.

High altitude flyers may suffer from a similar condition due to the escape of dissolved nitrogen from the blood in a rarefied atmosphere. In 1942 a sub-committee of the National Research Council undertook the study of "Decompression Sickness" as it affected flying personnel. This work has resulted in much new knowledge of the disease which is here recorded.

This book should be a useful reference work for the general medical reader, while the doctor in industry and particularly the Air Force Medical Officer, will find it a valuable addition to his library.

Ear, Nose and Throat Diseases for the General Practitioner By WILLIAM MCKENZIE, M B, B CHIR, F R C S Pp 136 Edinburgh E & S Livingstone 1952 Price 9s net

The term of this book suggests that it presents material from a short series of lectures. The first person singular recurs with irritating frequency. While allowance must be made for dogmatism in a work of this nature, exception could be taken to too many of the views expressed. It is definitely not for undergraduates.

The Use of Tracer Elements in Biology By W E OVEREND, PH D Pp iv+57 London Heinemann 1952 Price 3s 6d

The object of this series is to make available recent advances of knowledge which have not yet reached the textbooks. After a short introduction the author discusses the requirements for a tracer then goes on to describe the uses that have been made of tracers in biology. His final chapter on tracers in medicine is very stimulating and suggestive. This subject has a great future and every medical man should be familiar with its possibilities.

The English Pioneers of Anaesthesia By F F CARTWRIGHT Pp v+338, with 20 plates Bristol John Wright 1952 Price 21s

In this small volume Dr Cartwright, Anaesthetist at King's College Hospital, London, has written three excellent biographical studies of Thomas Beddoes, Humphry Davy and Henry Hill Hickman. Being himself of West of England stock and with forebears who had intermingled socially with Beddoes and Hickman, the author, not unnaturally, has had some additional stimulus to give vitality to his story. As a result of considerable research some new material has been elicited and certain mistaken conceptions concerning the original work of the three pioneers have been corrected. The thesis that their contributions to the development of anaesthesia have been underrated in the past is well sustained in a scholarly presentation of the scientific evidence against a background of personal histories which continuously holds the interest of the reader. Dr Cartwright's book is worthy of a place on the bookshelves of all doctors whatever their particular sphere of activity may be.

The Advance to Social Medicine By RENE SAND Pp 590, with an index London Staples Press 1952 Price 42s net

In this book Professor Sand not only describes the history of social medicine itself but gives a detailed account of the converging streams of medical thought and practice which have produced the broad flow of preventive medicine which we know to-day. There is no field upon which he does not touch, and he mentions most of the great medical figures of the past two thousand years and many earlier still. It is interesting and salutary to learn that some "modern discoveries" and recent health machinery are indeed old, for example, the sixteenth century health offices maintained in French cities to deal with epidemics, and the belief widely held in Africa and the East since earliest times that malaria was caused through a mosquito bite.

This compendious volume is packed with information, in fact, so rich a fare is offered that the book is one to dip into rather than to read straight through. In places the style suffers from over condensation, and this may also account for certain inaccuracies in the text. In the chapters dealing with contemporary preventive medicine, there are numerous references to the U S S R with, unfortunately, no details given, and the section devoted to international contributions to social medicine is inadequate. Nevertheless, this book is an important contribution to the history of medicine in general and social medicine in particular.

NEW EDITIONS

The Pharmacologic Principles of Medical Practice By JOHN C KRANTZ and C JELLEFF CARR Pp xvii+1116, with 95 figures Second Edition London Bailliere, Tindall & Cox 1951 Price 76s 6d

A new edition of this essentially practical American textbook has been called for after a period of only two years. As before, the arrangement of the subject-matter is based upon the physiological systems of the body, and the emphasis is placed on currently used drugs. The mechanisms of their actions and their clinical application are fully explained and discussed. Although the official American names differ in some cases from British ones this does not give rise to any great difficulty, and the book should prove both interesting and useful to students and medical teachers.

Obstetrical Practice By ALFRED C BECK, M D Fifth Edition Pp xiv+1073, with 947 illustrations and 22 reproductions of X-ray films London Bailliere, Tindall & Cox 1951 Price 76s 6d net

Much of this edition has been rewritten so as to incorporate the relevant new physiological and pathological knowledge and present the modern changes in opinion regarding the management of some obstetrical problems. The extensive bibliography at the end of each chapter shows the wide and varied reading which the author has moulded into his own experience and practice. The text is clear, reads easily and is liberally illustrated, indeed the mechanisms of labour and many of the operative procedures are depicted in a series of simple drawings executed by the author, and make for clarity of teaching and avoidance of lengthy descriptions. An interesting feature of the book is the reproduction of portraits of eminent obstetricians found at the end of many of the chapters.

The physiology of the foetus is described in detail, but with the exception of asphyxia, and the initiation of lactation, little reference is made to the newborn child and the commoner pathological conditions met with after birth. There is also little to be found on the vexed question of postmaturity apart from its occurrence in diabetes. To avoid confusion the reader in this country must remember that the definition and use of "presentation" is the traditional American one and corresponds to the British use of "foetal lie."

A Clinical Atlas of Blood Diseases By A PINEY, M D, M R C P Seventh Edition Pp vii+137, illustrated London J & A Churchill 1952 Price 21s net

This Atlas which first appeared in 1930 has long been regarded as a standard work. The essential features of the book is a series of 48 full-page illustrations, 45 of which are in colour. With each illustration is a short account of the disease covering all the important features. A further series of descriptions is given of conditions not illustrated. The work is beautifully produced and should be of the utmost assistance in the differentiation of blood disorders.

The Asthmatic Child By G F WALKER, M D, F R F P S G, D C H, M R C P Second Edition Pp 19, with 24 illustrations Bristol John Wright 1952 Price 2s 6d

This small brochure is addressed to the parents of asthmatic children. Two pages of general instructions are followed by a description of ten different exercises illustrated by a series of photographs. A useful publication.

Introduction to Clinical Neurology By GORDON HOLMES, M D, F R S Second Edition Pp viii+189, with 43 illustrations Edinburgh E & S Livingstone 1952 Price 12s 6d

From his vast experience as a clinical teacher the author has produced a book which outlines the essential background on which alone it is possible to build a proper understanding of nervous disorders

It is a book of symptoms and signs, and their explanation and significance in relation to present-day anatomical and physiological conceptions, and in this edition only a few additions have been required due to the increase in knowledge of these basic subjects

Methods of clinical examination receive a prominent place and many useful practical points are to be found Wisely, too, all mechanical aids to diagnosis have been excluded, impressing on the reader the importance of clinical methods founded on the basic principles so masterfully presented here

Internal Medicine Its Theory and Practice By J H MUSSER, B S, M D, F A C P Fifth Edition Edited by M G WOHL, M D, F A C P Pp 1503, with 236 illustrations and 10 coloured plates London Henry Kimpton 1952 Price 105s net

This edition, like its predecessors, presents in one volume a comprehensive survey of the entire field of internal medicine Many new subjects such as genetics, geriatrics, rehabilitation, psychosomatic disorders and the general adaptation syndrome are included in this latest edition Over eighty authors have contributed sections in their own special branch of medicine This book can be thoroughly recommended to both student and post graduate

The Practitioner Handbooks Practical Procedures Edited by SIR HENEAGE OGILVIE, K B E, D G, G C R, F R C S, and WILLIAM A R THOMSON, M D Second Edition Pp 380 London Eyre & Spottiswoode 1952 Price 25s net

Although this book is technically a second edition it has undergone such thorough revision and complete resetting that it is practically a new book Many new chapters have been added, dealing with such subjects as the administration of antibiotics, hormone implantation therapy, biopsy, and gynaecological and ophthalmological procedures This book provides sufficient detail of common procedures to allow the practitioner and hospital resident to carry them out or to know what is required if they are to be done by someone else Furthermore, it explains in detail the rationale of some procedures and should therefore prove of great value to practitioner and hospital resident alike

Approved Laboratory Technique By J A KOLMER, M D, S C D, D P H, F A C P E H SPAULDING, P H D, and H W ROBINSON, P H D Fifth Edition, with 403 illustrations and 28 coloured plates London H K Lewis 1952 Price 90s

In preparing this work the authors have had the assistance of a team of 18 experts This new edition is considerably enlarged and in great part rewritten It covers all fields of clinical laboratory work, bacteriology, serology, pathology and chemistry, including the detection of certain poisons Methods are described in great detail since no laboratory examination can be better than the thoroughness and skill with which it is conducted The authors also emphasise the care with which the clinician should take the specimen, and again describe in considerable detail the proper methods for collecting material for investigation

The book is a thoroughly sound and authoritative guide to laboratory examinations and can be highly recommended

BOOKS RECEIVED

The Tissues of the Body By W E LE GROS CLARK, FRS Third Edition Pp 11+407, with 124 illustrations Oxford Clarendon Press 1952 Price 30s net

The subject of anatomy is apt to be regarded merely as a study of topography—a description of the structural complexity of mature organisms Professor Le Gros Clark, however, in *The Tissues of the Body*, rightly emphasises the importance of the teaching of structural organisation as a dynamic process He stresses the relationship of structure to function, and frequently alludes to recent experimental investigations The sections on vascular patterns, muscle architecture, and mechanics and growth of bone are particularly interesting He states that in this introduction to the study of anatomy he has endeavoured to provide intellectual stimulation, and he succeeds brilliantly

BOOKS RECEIVED

ARMSTRONG, HARRY G, MD, FACP Principles and Practice of Aviation Medicine (Baillière, Tindall & Cox, London) 57s 6d net

ARMSTRONG, J R, MD, MCH, FRCS Lumbar Disc Lesions (E & S Livingstone Ltd, Edinburgh) 42s net

BARRON, S L, and SCHOTT, A, MD (HEIDELBERG), MRCS Cardiographic Technique (William Heinemann, London) 21s net

BRITTAIN, H A, OBF, MA, MCH, FRCS Architectural Principles in Arthrodesis Second Edition (E & S Livingstone Ltd, Edinburgh) 42s net

FLOREY, M E, MD The Clinical Application of Antibiotics Penicillin (Oxford University Press, London) £4, 4s net

GARDNER, ERNEST, MD Fundamentals of Neurology Second Edition (IV B Saunders, Company, London) 24s

GRAY, JAMES, MA, FRSE History of the Royal Medical Society, 1737-1937 (The University Press, Edinburgh) 42s net

Edited by GUTHRIE, DOUGLAS Logan Turner's Diseases of the Nose, Throat and Ear (John Wright & Sons, Bristol) 42s

LÉPESCHKIN, EUGENE, MD Modern Electrocardiography The P Q R S T U Complex (Baillière, Tindall & Cox, London) post 1s 1d

LEYTON, NEVIL, MA (CANTAB), MRCS, LRCP Migraine and Periodic HEADACHE (William Heinemann, London) 9s 6d net

MAINLAND, DONALD, MB, CHB, DSC, FRSE, FRSC Elementary Medical Statistics (IV B Saunders Company, London) 12s 6d net

MAXIMOW, ALEXANDER A, and BLOOM, WM A Textbook of Histology Sixth Edition (IV B Saunders Company, London) 25s

Edited by MILLER, SEWARD E, MD A Textbook of Clinical Pathology Fourth Edition (Baillière, Tindall & Cox, London) 50s

PAUL, HUGH, MD, DPH The Control of Communicable Diseases (Harvey and Blyth Ltd, London) 68s 6d net

SALTER, WILLIAM T, MD A Textbook of Pharmacology (IV B Saunders Company, London) 55s

SCOTT BROWN, W G, CVO, MD, BCH, FRCS Diseases of the Ear, Nose and Throat Volume I (Messrs Butterworth & Co Ltd, London) 75s

Edited by SCOTT BROWN, W G, CVO, MD, BCH, FRCS Diseases of the Ear, Nose and Throat Volume II (Messrs Butterworth & Co Ltd, London) £8, 8s per set

Surgical Forum Committee Surgical Forum (IV B Saunders Company, London) £8, 8s per set

TIDY, NOLL M Massage and Remedial Exercises in Medical and Surgical Conditions Ninth Edition (John Wright & Sons Ltd, Bristol) 50s

WELLS, CHARLES Prostatectomy A Method and its Management (E & S Livingstone Ltd, Edinburgh) 27s 6d

Edited by WILLIAMS, P O, MA (CANTAB), MB, BChIR, MRCS, LRCP Careers in Medicine (Hodder & Stoughton Medical Publications, London) 24s net

15s net

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SURGICAL EMERGENCIES OF INFANCY

By F H ROBARTS, M B, F R C S Ed

Assistant Surgeon, Royal Hospital for Sick Children, Edinburgh

INTRODUCTION

" I PRESUME not to write of things which I never had an experience of—those I leave unto wiser men " These words were written by Felix Wurtz, a Swiss surgeon of the sixteenth century and author of *The Children's Book*—the first treatise on Infantile Surgery

I too intend to refer only to those things of which I have had experience There are few surgeons in this country who are concerned with the surgery of the infant and the child alone, and many general surgeons, on occasion, are faced with the problems of surgery in the infant, the clinical approach to which differs considerably from that in the adult

The broad headings for the conditions which will be discussed are as follows —

A *Congenital deficiencies of the parietes of the body cavities*

- (1) Of the abdomen
- (2) Of the cranium and the vertebral canal

B *Alimentary conditions*

- (1) Obstructions
- (2) Obstruction with fistulous communications
- (3) Obstructions sometimes associated with hæmorrhage from the bowel
- (4) Hæmorrhages from the bowel sometimes associated with obstruction

C *Infective conditions*

D *Genito-urinary emergencies*

E *Foreign bodies in the natural passages of the body*

Traumatic conditions have been omitted purposely first, because the infant is less often exposed to injury, secondly, because treatment differs little from that founded on basic principles and applied to all ages

A Honyman-Gillespie Lecture delivered in Edinburgh on 1st November 1951

GENERALITIES

Before approaching the clinical and technical aspects of surgical emergencies in infancy, it may be profitable to mention some *important generalities*

History and Clinical Examination—In adults, the history is obtained directly. The infant is often brought to hospital by a junior nurse, by an obliging but ill-informed neighbour, or by an anxious grandmother. Mothers vary in intelligence and composure. The doctor's letter seldom contains all the information desired. Records from other hospitals should be invaluable, but only if accurate and truthful. Therefore the data of a history have to be sifted with considerable care, and every detail of the clinical examination assumes great importance. Co-operation from an infant is entirely lacking and although there should be method, opportunities must be seized quickly as they occur. If it is causing distress to an ill child the examination must be brief though punctilious. Firm decisions are desirable. Diagnostic doubts are seldom resolved by continued examination, and searchings for further signs portend greater confusion. These are general principles whose importance is enhanced for the pædiatric surgeon.

Radiological Investigation—The chief ancillary to the clinical examination is an appropriate radiological investigation. This procedure is particularly helpful in the alimentary obstructions. Straight "scout" films of the abdomen are preferable, for they cause little upset to the child. Sometimes it is imperative that a contrast medium should be used. Vomiting and regurgitation endanger the infant with obstruction by aspiration of the vomit into the lungs, where barium sulphate produces a severe and often fatal pneumonia. Lipiodol, in minimal quantities, is satisfactory and eliminates this risk. As a "follow-through" medium in cases of doubtful obstruction it can be a very useful agent.

In cases of spina bifida, which by the clinical examination may have been adjudged suitable for operation, an X-ray of the skull will often show the lacunar areas of bone porosity which attend a degree of hydrocephalus. This is a feature which precludes a satisfactory outcome from operative correction of the spinal deformity.

Vomitus—Certain bed-side and side-room examinations are also of considerable value in diagnosis. An inspection of the vomitus is always of interest. In congenital hypertrophic pyloric stenosis the absence of bile is a useful sign, of greater importance are the amount of the gastric residue and the time relationship of the specimen to the previous meal. The amount of mucus in the specimen is an indication of the severity of the accompanying gastritis. This influences the nature of the pre-operative treatment. In duodenal atresia and volvulus neonatorum, frequent vomiting of a bile-stained fluid in association with visible gastric peristalsis occurs. In all obstructive states gastric

suction is an indispensable safeguard against asphyxia, pneumonia and atelectasis

Meconium and Stool—An examination of the stool or of material obtained on rectal examination is of interest and importance. Even in intestinal atresia a considerable quantity of meconium may be passed and this may be little changed in appearance from the normal, though usually it is less bulky, paler and more inspissated. When the alimentary tract is entirely patent vernix cells from amniotic fluid swallowed *in utero* are always found in meconium. In intestinal atresia they are not demonstrable in a suitably stained smear preparation (Farber, 1933). Blood and mucus, both in moderate quantity and without faeces are found typically in the majority of cases of acute intussusception. Blood in quantity without mucus suggests enteric ulceration such as may occur in association with a Meckel's diverticulum, with heterotopic islets of gastric mucosa, or it indicates intestinal duplication. Blood with a foul stool and severe toxæmia may occur in acute gastro-enteritis, and blood in association with bruising may point to an acute scorbutic condition or hæmophilia.

Pre-operative and Post-operative Care—In recent years considerable advances have been made in measures for the pre-operative and post-operative care and sustenance of infants. However, it is quite true that an infant who is full-term, strong and healthy in all respects other than its congenital anomaly, will tolerate operative intervention of a major degree. Once this initial advantage has been lost by delay, and the temporary decline of the first week of life and the effects of an anomaly allowed to develop to a severe extent, this resistance to trauma, developed for the supreme stresses of birth, disappears.

The fluid and electrolytic balances of an infant are rapidly disordered by dehydration and over-hydration. Great care must be exercised in parenteral administrations of fluids, with a total blood volume in the new-born of only 300 to 400 c c, or in the child of a year of 600 c c, overloading can easily occur. The daily fluid requirements of such infants are in the region of 450 and 1000 c c respectively. As a general rule, if a child is in urgent need of fluid, 15 c c per pound of body-weight may be given as an infusion, if blood is required, the transfusion volume can be estimated at not more than 10 c c per pound of body-weight.

The value of chemotherapeutic agents both prophylactically and therapeutically needs only to be mentioned. In the very young child there is little place for the use of other drugs, but adequate sedation of the older infant is just as important as it is for the adult. Heroin gr 1/96 has always been found satisfactory and reliable. Phenobarbitone gr 1/2 to 1 produces a lighter and more prolonged effect. Hypoprothrombinæmia develops rapidly in any ill child whose natural intake is reduced, the routine administration of vitamin K analogue is desirable for its anti-hæmorrhagic effect and for the ensuring of sound wound-healing.

Anæsthesia—The advances of modern anæsthesia and their application by anæsthetists skilled in this work have contributed more than anything else to the improvements in mortality figures, and permit more formidable procedures. General inhalation anæsthetics administered with closed-circuit apparatus adapted to the small and feeble respiratory excursion of the infant are most satisfactory. Even intratracheal administration and positive pressure with controlled respiration are obtainable for intra-thoracic work, and with care there is little risk of pressure effects upon the delicate tissues of the larynx and the lungs. In abdominal work spinal anæsthesia and the relaxant drugs are not considered safe or suitable for the infant.

The discussion of these preliminary basic matters is important for it is upon a full understanding of them that the success of any surgical procedure depends.

CONGENITAL DEFICIENCIES OF THE PARIETES OF THE BODY CAVITIES

Congenital deficiencies of the parietes of the abdominal cavity are the most important and include the following and related conditions which will require urgent surgical treatment.

- (1) Congenital umbilical hernia or exomphalos
- (2) Irreducible inguinal hernia
- (3) Torsion of a testis—usually related to incomplete descent and to association with an inguinal hernia
- (4) Torsion or strangulation of an ovary in association with an inguinal hernia

Exomphalos—Exomphalos is a condition which is evident at birth. More than the usual care should be exercised in the ligation of the cord so that no content of the hernial sac is ensnared. By inspection of the transparent sac the nature of its visceral content can be made out. A large amount of visible liver and a broad base of over 7 cm. will suggest that difficulty may be encountered in obtaining sound closure at the initial attempt. Provided that no other serious congenital anomaly exists, operation should be performed at the earliest opportunity, with delay, the amniotic covering dries and is more liable to rupture, the alimentary tract becomes filled with swallowed air and closure becomes more difficult. Disaster will come with attempts to pack viscera tightly into the small abdominal cavity. It is dangerous to deepen the anæsthesia to assist in this process. If the fascial edges and peritoneum cannot be united easily, further dissection of the skin and superficial tissue will allow of their approximation, the large mural defect which remains being repaired secondarily after the lapse of two to three weeks when the abdominal cavity has enlarged (Gross and Blodgett, 1940). Then there is no longer any danger of causing cardiac and respiratory embarrassment or intestinal obstruction by the production of undue intra-abdominal pressures. When the defect

is large it has been suggested that no attempt should be made to excise the hernial sac. The coverings are rendered as sterile as possible by bland antiseptics and the skin is widely mobilised from around the point of junction with the sac, which can then be covered entirely by this skin. Thus adequate protection is obtained until a second operation for the repair of the very large umbilical hernia is performed (Gross, 1948).

Irreducible Inguinal Hernia—Inguinal hernia from patency of the processus vaginalis is of very common occurrence. To a lesser extent is such a deficiency found in respect of the canal of Nuck in the female. Irreducibility of hernial content occurs in a proportion of these cases. The term "irreducibility" is used advisedly for strangulation of bowel is unusual though not unknown. This complication occurs more often in the premature child and sometimes at the first appearance of the hernia. Under the age of three months delay is desirable in advocating operative treatment of the uncomplicated inguinal hernia for spontaneous cure may occur. Irreducibility is an indication for more immediate operation. The actual diagnosis of the condition seldom presents much difficulty, but a tense and encysted hydrocele of the cord may simulate it. It is usually possible to feel the upper limit of a hydrocele in the cord. If there is any uncertainty, in cases of irreducible hernia it will be found that tender enlargement of the corresponding testis has occurred from interference with its venous return. Considerable œdema of all the cord structures below the obstruction occurs rapidly, and in tissues which are already often tenuous and delicate, this is a change which makes definition of the sac at operation more difficult. It is because of this that attempts to obtain spontaneous reduction should be made. Direct taxis is seldom successful, distresses the child and may be dangerous. Sedation with chloral hydrate gr 2 to 5, according to age and size, is the most important factor in obtaining reduction. This may be assisted by raising the foot of the cot, by flexing the thigh on the affected side, and by the application of warmth. Should these methods fail after two hours' trial, operation becomes essential. When they succeed, a short delay is permitted for the absorption of œdema, and operation is performed before the child goes home. Some irreducible herniæ undergo spontaneous reduction, or can be reduced manipulatively under the general anæsthetic, the operation can then be carried out as for the simple case, without opening the inguinal canal. At this age the irreducible hernia differs from that in the adult in that the obstructing agent is usually the external and not the internal inguinal ring. If the irreducible state persists, an obliquely placed incision becomes necessary so that the external oblique aponeurosis can be exposed, the canal opened and the constricting external ring divided from above downwards. The usual precautions must be taken to secure the hernial content for inspection of its viability before it is allowed to return within the abdominal cavity. The hernial sac is then excised.

in the usual manner, though this may be difficult in the vaginal type where the testis dangles from its mesorchium within the sac and the vas and vessels appear to be an integral part of its wall. It is this type which is often encountered in the premature child.

Torsion of the Testis—It is the vaginal type of hernial sac which so often accompanies undescend of the testis, and such a testis hanging by its mesorchium in this potential space is the one in which torsion may occur. The abnormal position with consequent exposure to external forces and to the stresses of muscular contractions are the factors which produce torsion. The onset of symptoms is sudden, and examination reveals a tender lump in the region of the external inguinal ring or of the canal itself. The testis is absent from the scrotum, as may be its fellow also, if the testis is more fully descended it is painful and swollen, but the higher lump of an irreducible hernia is absent. The differentiation from an acute epididymo-orchitis then arises, and if any doubt exists it is safer to operate. Unless the torsion is undone within a few hours of its onset, irreversible changes in the testis occur which make orchidectomy necessary. With bilateral undescend of the testes in which torsion on one side and subsequent orchidectomy have occurred, there is a risk that similar events may occur in the remaining testis. At this stage it is often found impossible to bring that testis down into the scrotum. Any attempt to achieve this may cause testicular atrophy. The minimum of operative disturbance is desirable, and it is recommended that even cure of the hernia be left until a later date, but that the mobile testis be immobilised by "button-holing" it through the wall of the sac and the coverings of the cord in the position where it already lies.

In the female, similar complications of an inguinal hernia may arise. An ovary may prolapse, become incarcerated and even strangulated, or may undergo torsion. Such incidents are corrected by the same methods which apply to the male.

CONGENITAL DEFICIENCIES OF THE CRANIUM AND VERTEBRAL CANAL

Spina Bifida—Of the anomalies which affect the skull and vertebral canal the degrees of spina bifida are the commonest. In the past, valiant attempts to repair these defects have been made. Usually meningoceles with a small defect were and still are amenable to surgical correction, where nerve tissue is present outside the spinal canal, as in the commonest degree of myelomeningocele, it is seldom possible to effect a cure which will remain satisfactory. Even where there does not appear to be any paresis of the lower limbs or urinary or anal incontinence and no obvious or radiological signs of hydrocephalus, some if not all of these features will almost certainly appear eventually, leaving the child an uneconomic responsibility to the parents or to the community. Unless the type of the deformity is simple and uncomplicated surgical correction is not advised.

ALIMENTARY ANOMALIES

It is the anomalous conditions of the alimentary tract which provide the greatest variety of surgical emergencies of infancy. Acute intussusception is not rare, and although it is an acquired condition, in some cases, there are minor anomalies which seem to contribute to its development. Other acquired conditions of this system are all relatively uncommon.

INTESTINAL OBSTRUCTIONS

This group includes —

- (1) Congenital hypertrophic pyloric stenosis
- (2) Intestinal atresia and stenosis
- (3) Intestinal malrotations and volvulus neonatorum
- (4) Meconium ileus
- (5) Hirschsprung's disease
- (6) Imperforate anus

Congenital Hypertrophic Pyloric Stenosis — In cases of congenital hypertrophic pyloric stenosis, the details of history and clinical findings are well known. Gastric peristalsis is not pathognomonic of the condition. It is always desirable to palpate the pyloric tumour before deciding upon operation. It is not always felt easily, sometimes it is relaxed. More frequently, the large and hypertrophied stomach overlies the tumour and masks it. The tumour never feels as large as it is found to be at operation. Operative treatment is now almost universally accepted by pædiatricians. This should be carried out within twenty-four hours of the diagnosis having been established, unless the child is very unfit and requires longer for the correction of its metabolic disturbances and amelioration of its gastritis by lavage. Rammstedt's operation leaves nothing to be desired in its effectiveness. Accidental opening into the duodenum is an event which will happen to most surgeons at some time, the possibility can be lessened by the meticulous termination of the initial pyloric incision at the distinct lower limit of the tumour and by gripping the duodenum immediately below the tumour, evaginating it from the duodenal fornices while the incision and the muscle separation are being performed. The operative mortality is now very low as a result of the appreciation by pædiatricians of the value of early operation and of better preparation for operation. Also of great importance are the more general use of light inhalation anæsthesia in support of regional local infiltration, and isolation from the risks of respiratory and alimentary infections.

Atresia and Stenosis of the Intestines — Atresia and gross stenosis of the gut produce obstructive symptoms within the first days of life. Minor degrees of stenosis seldom present as urgent conditions. The site of the lesion modifies the symptoms and the clinical findings: the higher, the more acute is the onset, and the more rapid the deterioration, less evident are distension, ladder patterning and

visible peristalsis. Straight films of the abdomen are of great help in assessing approximately the level of the obstruction, and usually aid in distinguishing these cases from obstruction due to a volvulus of the mid-gut loop. The vernix test upon the meconium is an additional help.

The treatment of these anomalies must be operative and mortalities are still very high. It is important to remember that the lesions are not infrequently multiple and a thorough search of the whole gut is necessary. Gross distension renders this inspection difficult, and evisceration is justifiable in order that time may be saved and mistakes avoided. Decompression of dilated loops by large-bore needle puncture and suction may be required for the replacement of the coils within the abdomen. The obstruction must be overcome by anastomosis, in the upper half of the duodenum by gastro-jejunosomy, and in its lower half by that procedure or, preferably, by duodeno-jejunosomy. In the infant entero-anastomosis should if possible be done by the end-to-end or end-to-side techniques. Although great care may be taken to keep the blind loops of a side-to-side junction as short as possible, with normal growth they can increase to form considerable cul-de-sacs, especially on the proximal side. These may cause troublesome symptoms in later life. In the circumstances of atresia direct end-to-end anastomosis is quite impracticable because of the marked difference in calibre of the loops to be united. Decompression of the proximal loop by puncture or enterotomy may reduce this to some extent. It is in the minute distal loop that most trouble is encountered. Its lumen is very small and suturing can reduce this dangerously. Its calibre can be increased artificially by injection of saline or air into it through a hypodermic needle. Anastomosis in two layers is not always possible, and it may be necessary to be content with one layer of interrupted silk sutures, which will allow free growth of the stoma.

These technical difficulties and the poor healing qualities of the proximal loop, whose viability is impaired by distension and partial volvulus, make disruption of the suture line a frequent complication. Resection of the proximal loop secures healthier bowel of greater strength and of more equal calibre for an anastomosis. Resection also removes a considerable amount of tenacious bowel content which can perpetuate the obstruction in the contracted distal bowel after anastomosis.

If there are several zones of atresia, the anastomosis will be performed with the first unobstructed portion of bowel. The atretic closed loops which have been by-passed should be left to be removed subsequently, they will cause no immediate trouble, though they may well do so by distension if allowed to remain indefinitely. Where the occlusion is by a diaphragm across the lumen of the bowel, it may be practicable to resect the greater portion of this through an enterotomy wound with closure of this transversely.

In the immediate post-operative period there is concern for the ability of the hypoplastic bowel below the anastomosis to increase its calibre. At operation dilatation may be encouraged by the injection

of saline in sufficient quantity to flow round to the rectum, subsequent passage of meconium through this portion of bowel may be encouraged by the injection of mineral oil into the lumen of the gut. After operation distension of the large bowel may be further stimulated by saline enemata. No mention has hitherto been made of ileostomy for the relief of obstruction. This has only an occasional use in the very ill child. Temporary improvement may then be obtained, but deterioration will very soon return and further measures for reconstitution of the bowel continuity must be undertaken.

Rotational Anomalies—It is well known that acute obstructive states can develop from rotational errors of the mid-gut. It is not always appreciated that a dual pathology often underlies the obstruction. The incomplete descent and fixation of the cæcum into the right iliac fossa result in an inadequate attachment of the mesentery of the whole small bowel to the posterior abdominal wall. The base of the mesentery is short and transverse, for the cæcum lies near the second part of the duodenum. Peritoneal reflections pass from the cæcum to the lateral aspect of the duodenum. The weight of the mid-gut may be sufficient to drag these peritoneal folds tightly across the duodenum. This simple cause of obstruction can operate from soon after birth, but more frequently symptoms of a periodic and less acute nature result. When a volvulus of the mid-gut occurs, the obstruction becomes two-fold, the traction across the duodenum is intensified, and the whole mid-gut becomes closed. This obstructive mechanism usually operates soon after birth, hence the term *volvulus neonatorum*.

Usually within two or three days of birth acute obstructive symptoms from these anomalies become very evident. The vomit contains bile, but obvious gastric distension with visible peristalsis may be absent through the efficacy of the vomiting. Abdominal distension depends upon the presence of volvulus and the degree of distension of the coils involved, if seen at an early stage these may be collapsed, later to distend with increasing bacterial putrefaction within them. Considerable help may be got from a straight X-ray of the abdomen. Duodenal distension ceasing abruptly in its second part, and gas in very little or varying amounts in the central area, with evidence of free fluid between the bowel coils, are strong evidence of this obstructive condition.

At operation, transverse incisions give excellent access and immediate appreciation of the exact nature of the obstruction is gained from the nature of the presenting coils of bowel. If there is much free fluid within the peritoneal cavity and if distended loops of small bowel present, there is a state of volvulus, which requires complete eventration of the child's gut to permit of its rapid reduction and inspection for the probable secondary causes of obstruction around the duodenum itself. Reduction is affected usually by rotation of the whole of the mid-gut in an anti-clockwise direction. If the colon

presents itself on first inspection, there is no volvulus. Displacement of the mobile cæcum downwards and to the left exposes the second part of the duodenum. Obstructing peritoneal reflections are divided and the cæcum displaced into the left half of the abdomen (Ladd, 1933). If the remainder of the duodenum, now exposed, does not descend directly down the right side of the vertebral column, search must be made in the region of the ligament of Treitz for further extrinsic causes of obstruction. These, too, must be divided, either until the duodenum can be made to descend vertically in its remaining parts, or until a Ryle's tube in the stomach can be threaded on into the upper coil of jejunum, where it may with profit be allowed to remain temporarily (Glover and Barry, 1949). These manœuvres result in a relative lengthening and altered axis of the posterior attachment of the mesentery, and are sufficient to ensure against the recurrence of volvulus.

Meconium Ileus—The treatment of meconium ileus causes the pædiatric surgeon little satisfaction, first, because of the poor prognosis and, second, because the techniques at operation appear so crude. The underlying pathology, which can never be corrected, is a congenital fibro-cystic disease of the pancreas. This produces celiac-like symptoms if the child lives. Staphylococcal broncho-pneumonia is a frequent complication on account of similar changes in the bronchial mucous glands. In the history the hereditary trait may help to indicate the cause of the obstruction which appears soon after birth. The absence of meconium in the rectum, and its replacement by a small yellowish mucus plug, the peculiar hard feel of the abdomen, dull on percussion, and the radiological sign of intra-abdominal calcification are conclusive findings. The site of obstruction is usually found in the lower ileum, where there is a sudden change from dilated and hypertrophied obstructed gut to hypoplastic ileum, the proximal few inches of which contain firm nodules of inspissated calcareous material. The whole of the large bowel is a "microcolon". Volvulus, necrosis, and perforation of the distal dilated loop are not uncommon. The procedure which is usually advocated in order to overcome this obstruction is proximal enterotomy and through a catheter the washing out with saline of the inspissated material after it has been softened and broken up by external pressure. Injection of fluid onwards into the microcolon will confirm that the obstruction has been relieved and it will increase the calibre of the bowel for the passage of the tenacious meconium which is present above the actual level of the obstruction (Hiatt and Wilson, 1948). This is not a technically satisfying procedure, therefore, it is suggested that no less success might be anticipated by an anastomotic procedure as in atresia, difficult to perform, but less redolent of a plumber clearing a choked drain. The deficient ferment is supplied as pancreatin and is given into the bowel at operation and by mouth and by enemata afterwards.

Hirschsprung's Disease—Hirschsprung's disease causes trouble with the bowel function from the earliest days of life, whereas megacolon

from other causes is a condition acquired gradually in a gut which has previously functioned well. Hitherto attention has been focussed on the dilated portions of the colon. Recently it has been shown that the abnormality is situated in a contracted segment of bowel below the secondarily dilated and hypertrophied sections. In this hindmost narrow portion there is a congenital absence of the ganglion relay cells of the parasympathetic innervation (Swenson, Rheinlander and Diamond, 1949). Sympathetic predominance, with a failure of relaxation and incapacity for co-ordinated peristaltic activity, exists. The extent of the affected segment may vary from involvement only of the lower rectum or it may include the whole of the large gut, and in some cases even the terminal ileum. With a long section of the gut involved, obstructive symptoms develop soon after birth, whereas in the less affected cases the bowels may move sufficiently though reluctantly, with the gradual production of the secondary changes typical of the classical Hirschsprung's disease.

Acute obstructive symptoms in this disease can be found at two stages of the condition, first, they may occur in the neonatal period or, second, at a later date when the clinical picture is more readily recognised. In the latter, marked peristalsis and explosive borborygmi accompany an obstructive incident, and temporary relief may be obtained, if the narrow segment is short, by the passage of a rectal tube. Definitive treatment can be instituted later by colostomy, and rectosigmoidectomy (Stephens, 1950). In the neonate, the diagnosis and treatment are not so easily defined. The diagnosis is suggested by the inadequate passage of meconium, by increasing signs of low intestinal obstruction, by the small capacity of the rectum on digital examination and by X-ray investigation. Hitherto, these cases have been diagnosed usually as some form of organic obstruction, and at operation the surgeon has been perturbed by his inability to display any cause of that nature. However, in these cases it is possible to find a portion of the gut in which there is transition from the dilatation of obstruction to bowel of normal dimensions. The typical agenesis of the intramural ganglia has been found to exist in the undilated portions of the gut, usually extending for considerable distances—to splenic flexure, proximal colon or even into the terminal ileum (Forshall, Rickham and Mossman, 1951). The only treatment of any avail is external diversion above the site of the neurogenic obstruction. No neonate will tolerate a large exclusion of the colon, and far less so an ileostomy, even for a short time. Therefore, in these extensively involved cases it seems improbable that any curative operation can be devised.

Imperforate Anus—Four types of this condition are usually described. The first includes all cases of stenosis, which may be of only minor extent and present no acute problems, or they may be of severe degree with small external and ectopic openings. These cases may behave initially like complete imperforation but even the narrowest

channel, exuding only an occasional bead of meconium may, by persistent and regular dilatation, be enlarged into an opening capable of functioning normally (Browne, 1951). In the second degree, a persistent cloacal membrane occludes a normal anal canal. The perineal appearance makes this type readily recognisable. Cruciform incision of the membrane provides relief, but a fibrous stricture will inevitably develop unless regular bouginage is performed in the ensuing months. In the third degree, the rectum ends blindly at a considerably higher level, and not infrequently a fistulous communication with adjacent organs—bladder, urethra, or vagina—may exist. It is for this type and especially for those cases with fistula, that more radical measures are now advocated. Colostomy relieves the obstruction but renders any subsequent operation more difficult by fixation of the gut and by impairing later appreciation of a fistula. The distance of the rectum from the perineum can be estimated by radiography. If the distance is less than one inch, the blind end can be approached from below through the external sphincter muscle which is always present (Ladd and Gross, 1934). The pouch is often intimately fused with anterior structures, especially when fistulous communication co-exists. If operation is undertaken before there is much distension of the pouch, its definition may be rendered difficult by recession upwards as dissection proceeds. Because of these difficulties a combined abdomino-perineal operation is now being advocated (Rhodes, 1946, Norris, Brophy and Brayton, 1949). From above, fistulae are more clearly identified, and the pouch more easily and more completely mobilised. Approximation of it to the perineum is thus affected with less risk of retraction through tension, and stricture is avoided. The fourth type is the rarest and most dangerous for there is persistence of an occluding membrane within the anal canal or rectum. Externally the anus appears normal, but the total failure to pass meconium should call for rectal examination. Delay in recognition is frequent and obstruction is often present to a degree so marked that colostomy alone may be practicable.

ALIMENTARY ANOMALIES WITH OBSTRUCTION AND FISTULA

As described above Type III imperforate anus is often accompanied by fistulous communications, similar dual lesions are sometimes found in the œsophagus and in relation to patency of the vitello-intestinal duct.

Congenital Atresia of the Œsophagus with Tracheo-œsophageal Fistula—Various types of this anomaly occur, in the commonest of which the lower part of the œsophagus forms a fistulous communication with the respiratory tree in the trachea, at the carina, or with one of the main bronchi. The condition should be suspected in any newborn infant who persistently accumulates oral secretions, which periodically cause attacks of choking, frothing at the mouth and cyanosis. These symptoms are exaggerated by attempts to feed the child. The

careful passage of a firm and moderately large rubber catheter reveals an impediment to its progress into the stomach. This finding warrants immediate investigation. Only as much lipiodol as is necessary to outline the upper œsophageal pouch should be used, although a small spill over into the trachea can occasionally define the fistulous communication with the lower œsophagus. Sometimes it is preferable to confirm the presence of this and its level by bronchoscopy. A fistula can be confidently predicted on the radiographic appearance of air in the stomach.

At operation, general anæsthesia through an intra-tracheal tube is essential for the adequate maintenance of controlled respiration. In these infants the pleura is exceedingly thin and very easily "holed," either on the side of approach by the extrapleural route, or during mobilisation of the œsophageal segments on the contra-lateral side. The approach is by resection of the fourth rib on the right side. Where there is absence of gas in the stomach, indicative of atresia of the lower segment also, a left-sided approach may be used in order that œsophago-gastrostomy may be attempted if necessary—a formidable procedure at this age which has been successfully performed. Most surgeons (Bigger, 1949) advocate an extrapleural approach in order to limit any infective process which will follow a leak at the anastomosis—a not infrequent complication. That approach is time-consuming, and fails to achieve its object if the pleura is "holed." The transpleural approach is immediate and direct. Usually, the tracheal fistula is readily found on the posterior aspect of the lower trachea, but, if it is situated at the carina or in a bronchus, considerable difficulty may be encountered in defining the lower portion of the œsophagus. Mobilisation of the œsophagus should be limited in order to preserve its blood supply. The fistulous communication is divided and the tracheal end closed by ligature, which is safe if placed with care. The hypertrophied upper œsophageal pouch is found towards the thoracic inlet, a tube passed into it by the anæsthetist helps in its identification. A traction stitch placed in its fundus aids in the mobilisation on its deep aspect. An estimate of the practicability of anastomosis can now be made. Every millimetre of each structure is valuable, the avoidance of tension is most essential, and if the narrower lower segment can be invaginated into the wider upper pouch a firmer two-layer anastomosis is obtained. End-to-end junction may be all that is possible but the distal portion holds stitches poorly, and the risks of leaking are considerable. Fixation of the upper pouch to the prevertebral fascia with a view to taking tension off the suture line is inadvisable, for such fixation only submits it to greater stresses from respiratory excursions. Mediastinal and intrapleural drainage are wise precautions before closure of the chest. Depending upon the fears of the surgeon for his anastomosis, gastrostomy may be performed some hours later. In the most hopeful cases sterile feeds with antibiotics by mouth can be given after forty-eight hours. Post-operative difficulties are—leaking at the

anastomosis and the formation of fistulæ, intrathoracic and mediastinal sepsis, all of which render gastrostomy essential. In the later stages strictures may develop and require prolonged treatment by dilatation. However, this anomaly, once consistently fatal, can now be corrected.

ALIMENTARY OBSTRUCTIONS ASSOCIATED WITH HÆMORRHAGE

The discussion of emergency alimentary conditions concludes with mention of important lesions which combine obstructive and hæmorrhagic manifestations. The acquired condition of acute intussusception is not uncommon, but the urgent states produced by Meckel's diverticulum or an associated peptic ulcer of the adjacent bowel, by heterotopic islets of gastric mucosa, and by duplications of the gut, are much less frequently seen.

Acute Idiopathic Intussusception—The clinical picture of acute idiopathic intussusception is clear in the minds of most doctors. However, the history, symptoms and signs are by no means always true to type. The child does not always scream with spasmodic agony, it is often found to "girn" its discomfort into the pillow while wriggling on its hands and knees. The quiet intervals accompanied by pallor occur more consistently. Vomiting is not an early sign, but comes with increasing intestinal obstruction. Blood with mucus may not appear from the rectum for at least twelve hours and in subacute and chronic cases, not infrequently found in the slightly older child, it may not appear at all.

The clinical signs are also well established, but there are certain points worthy of emphasis. The commonest site for the palpable tumour is in the right hypochondrium. Here it can be masked under the projecting liver of the infant, and all infants object to pressure on the liver. The tumour is most easily palpated when it is hardest. Then, during an attack of pain, the examination is more difficult. A fleeting impression of the presence of a tumour in this region is sufficient to warrant operative measures. When present in the left half of the abdomen there is never any difficulty in feeling the tumour. Its bulk is larger and tension on the mesentery has drawn it towards the umbilicus. The presence of the tumour in the rectum is by no means of serious prognostic import, rapid progression often results in relatively easy reduction. Failure to advance often implies early tension on the mesentery. This is an important factor in the production of the changes which lead to irreducibility. The *Signe de Dance* of "palpable emptiness" in the right iliac fossa is most unreliable. When the tumour is proximal to the splenic flexure rectal examination may not reveal any blood or mucus, but simultaneous abdominal palpation along the line of the colon from the suspected tumour towards the rectum may reveal this latent sign. Unless the surgeon is an exponent of the hydrostatic method of reduction of intussusception, barium enema investigation is seldom necessary. This method of treatment is eminently successful in the hands of many surgeons, but

direct surgical measures are ultimately safer, and cannot ever be entirely avoided

Intussusception is an intestinal strangulation and if much blood has been lost it should be replaced. When the reduction is difficult gentle dilatation at the neck of the tumour with the little finger, and gentle traction upon the entering loop are as much as is permissible. No longer than five minutes should be given to attempts at the reduction of a stubborn tumour, and no other operative procedures to encourage reduction should be done. Most tumours will reveal their irreducibility before this lapse of time. Resection and end-to-end anastomosis do not now have a high mortality and experience has shown that it is often in the interests of the child to proceed to resection, even although persistent and prolonged manipulation might in the end achieve reduction. There is no certainty that the intussuscepted area will then be found viable, and even if it is so, the post-operative course of these children is often complicated, and a fatal outcome is not unusual. It is possible that this may be due to the absorption of katabolic products, analogous to those found in the "crush syndrome."

In the face of irreducibility there is no doubt that resection is the procedure of choice. It is at once curative and final. In the very ill child, exclusion, exteriorisation, or even ileostomy have been performed. Although successes have been achieved by these means, early resection in the case of exclusion, and early reconstitution of the bowel in exteriorisation and ileostomy are essential. But these are major procedures which throw an additional strain upon an already weakened child. The frequent finding of undue mobility of the cæcum and ascending colon renders resection relatively easy and an aseptic two-layer anastomosis does not take long. Therefore, resection is recommended with confidence.

Meckel's diverticulum—Persistence of vitello-intestinal ductal tissue—more often called Meckel's diverticulum—is the commonest of the anomalies of the gastro-intestinal tract. Complete patency of the duct at the umbilicus is seldom urgent unless atresia of the ileum exists below. Closure, but with persistence of intestinal mucosa at the umbilicus, produces a "mulberry tumour" (enteroteratoma), the history of which in earlier life is a useful pointer to a Meckel's diverticulum in any patient with acute abdominal symptoms in later life. Such a diverticulum may never cause symptoms, but if it has attachment to the anterior abdominal wall at the umbilicus, the risk of intestinal volvulus is ever-present and may arise at any age, though it is relatively infrequent in infancy, also, hæmorrhage from ulceration of the intestinal mucosa adjacent to the diverticulum may occur at any age but, relatively, this is quite often encountered in the infant. This ulceration is produced by the secretion of islets of gastric mucosa within the diverticulum. Such islets may occur in other sites of the bowel with the production of similar vague symptoms of recurring abdominal pain, sometimes related to the taking of food. The urgent

symptom, however, is rectal bleeding which, usually preceded by minor incidents, is often profuse and can be exsanguinating. Resection of the affected segment and the diverticulum is indicated. It is doubtful whether acute Meckel's diverticulitis ever occurs as a bacterial process; such cases are almost certainly due to ulcer and the associated reactionary changes. Perforation is a rare complication of the clinical picture, adhesion and obstruction are more common. A freely mobile diverticulum can tie itself into the most intricate knots, often ensnaring bowel loops in the tangle. Such obstructions, complicated by strangulation, are straightforward in their diagnosis and treatment.

Intestinal Duplication—Duplication of portions of the alimentary tract is probably the rarest anomaly of this system. It arises from a double recanalisation of the intestinal tract after the solid stage of the sixth and seventh embryonic weeks. Duplications are an inherent part of the intestinal tract and occur most often in the ileum. The duplicated portion may be very short, less often it extends over a considerable length of the gut. Symptoms are caused by those which are closed completely off from the normal bowel. Lined with normal mucosa, a cyst is formed by gradual distension with secretions. Although true mesenteric cysts do occur, there is no doubt that in the past duplications have been mistaken for these. The distinction is important, for a cyst can often be enucleated, but the muscular wall of a duplication is intimately fused with the associated normal gut and removal cannot be accomplished without damage to that structure and its blood supply. Resection of the abnormal portion is essential. Symptoms are caused, either by increase in size interfering with the blood supply to the main tract, or occluding the lumen of the normal tract. In the first instance, extravasation of blood occurs into the intestinal tract. Warning bleedings may occur, but the hæmorrhage may be considerable. Obstructive symptoms from occlusion are of an increasing nature. The two pictures are not infrequently combined, one predominating over the other. It is usual for a duplication to cause trouble relatively early in life, and on examination a mobile and possibly spherical tumour may be felt within the abdomen. Within the thorax, in the pelvis, and when related to the stomach, the symptoms are due to the effects of pressure upon the neighbouring organs. Excision may be less urgently required, though inevitably essential.

INFECTIVE CONDITIONS

Umbilical Sepsis—In the neonate sepsis at the umbilicus is less frequently encountered than previously, but the dangers of peritonitis, liver abscess, and septicæmia still exist, although their control is now more effectively obtained. A distant and crippling complication of this same focus of infection is arthritis of a major joint, usually at the hip. Early recognition, when the damage could be limited, is not easy, for, in common with other acute infective processes in early life, the general body response is weak and undemonstrative.

Osteomyelitis—In the infant, osteomyelitis of the classical type is unusual, but infection is not infrequently encountered in the jaws, and especially in the maxilla. The infection is thought to arise in the tooth follicles. Extension upwards to the orbit sometimes produces alarming displacement of the ocular globe itself, and evacuation of such an abscess may be urgently required.

Acute Appendicitis—In childhood, acute appendicitis is a common disease. In infancy, although it is not unknown at quite an early age, it is generally seldom encountered under the age of two years. Delays in the diagnosis are common, and peritonitis is frequent. The treatment at all stages of the disease is operative, and it is a matter of recurring interest how smooth and uncomplicated is the usual post-operative course of the very young. More often it is an older child and a male who succumbs to the complications of toxæmia, paralytic ileus or organic intestinal obstruction.

URO-GENITAL CONDITIONS

In infancy, emergency conditions of the urogenital system are few. *Injuries* are seldom sustained at this age, but it is important to remember that the infant's bladder, even when empty is an intra-abdominal organ. Damage to the kidneys or ureters, which are surrounded by little fat and covered by a tenuous peritoneum, may be associated with peritoneal contamination. *Renal infarction* of a type peculiar to the very young is a condition for which urgent treatment may be necessary. Considerable dehydration may permit spontaneous thrombosis of one or both renal veins, and massive venous infarction may arise in the course of a severe pyelonephritis. Blood and pus appear in the urine and the enlarged organ or organs are easily palpable. For unilateral involvement, nephrectomy can be curative. As parenteral pyelography at this age is not always satisfactory, at operation, proof of the second and adequate kidney is obtained by direct palpation of it across the peritoneal cavity.

Perhaps *meatal ulcer* is not a true surgical emergency, but it is certainly a social one. In the circumcised child this simple condition can produce the most acute pain and with the associated ammoniacal dermatitis of the napkin area causes marked irritability. At night, these manifestations are always most severe. The remedy for the distressed child and his parents is simple (Hamilton and Middleton, 1927). Impregnation of all napkins with a saturated solution of boracic acid prevents the bacteriological splitting of urea and the formation of ammonia. *Paraphimosis* seldom arises in the infant unless from the ill-advised and unnecessary retraction of the prepuce. Each baby boy is born with an irretractable prepuce, which if left entirely alone will enlarge adequately at its orifice. Retraction only opens up prematurely the preputial sac in which infection may thereafter occur and small tears in the prepuce itself are caused and lead to scarring and phimosis. True congenital phimosis is rare, and with

this and ritual the only criteria for circumcision are—fibrotic phimosis, recurrent balanitis and paraphimosis

FOREIGN BODIES

Of foreign bodies in the natural passages of the body little needs to be said. In the alimentary tract it is important not to rely only on a film of the abdomen for the revelation of a swallowed metal object, a neck and chest film is of even greater importance. It is impaction in the pharynx or œsophagus, and entrance of the foreign body into the respiratory tree that are of urgent significance, and urgent symptoms are not always evident in these circumstances. A negative abdominal film alone may mislead dangerously. In the stomach or intestine early surgical removal is indicated for objects over two and a half inches in length, especially for those that are sharp-pointed. Operative removal is required of any object retained in the stomach for three weeks, or delayed in passing on in the duodenum or lower reaches of the gut for more than three days.

CONCLUSION

That this work amongst infants is rewarding will be appreciated especially by those whose chief concern is with the adult and the ageing, in whom the problem is often that of disease and the degeneration of an unresponsive body. The latent attributes of an infant rescued by surgery are relatively unlimited and certainly unknown. The presence of these children as they grow in stature and develop in mind is a recurrent joy and stimulus therefore, in this world of lowered values, even ethical and moral, I ask in all humility—Is the saying not still true?—

“He stands the straightest who stoops to help a child”

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OBSERVATIONS ON THE ÆTIOLOGY OF BRONCHIECTASIS

By N WYNN-WILLIAMS

From the Bedford General Hospital and Chest Clinic

A STUDY of the literature of bronchiectasis shows that the majority of surveys have been conducted either on the selected material which finds its way to the large hospitals or on groups of individuals, nearly all male, who have been singled out for military service. It is also apparent that certain of its aspects have received greater attention than others. For this reason I have conducted an inquiry into the ætiological factors of bronchiectasis over an area in Bedfordshire where a survey can be arranged to cover most cases of the disease, both those already proven and those requiring diagnosis. This area is sufficiently far from a large centre for the local hospital to be the natural place of reference, but not so remote as to preclude reasonable facilities for investigation. Any inquiry into the ætiology of such a chronic condition, in which a long interval usually passes between the onset of symptoms and the date of diagnosis, offers special difficulties in obtaining an accurate history, particularly if one is dependent on the memory of the patient or that of an older relative for past events. The many acute diseases of infancy and childhood, which are apt to follow each other very quickly, also render it hard or impossible sometimes to decide which was responsible for the damage to the bronchi. Great care has been taken to secure as exact a history as possible, a number of old medical records both of hospitals and general practitioners have been of much help in this direction. The following brief case report illustrates how unreliable the information given by a patient or his relations may be.

A boy aged 10 was referred in 1949 because of persistent cough following a cold. A radiograph showed slightly increased pulmonary markings in the right middle zone with questionable hilar calcification. Pertussis followed by cough for about nine months was the only relevant illness reported during his previous history. Later a radiograph taken in 1944 and the results of investigations at another hospital became available. They proved conclusively that he had suffered from primary tuberculosis and that successive films had shown only partial clearing of the lesion. A bronchogram (Fig 1) in 1951 confirmed the presence of bronchiectasis which might with justice have been attributed to pertussis.

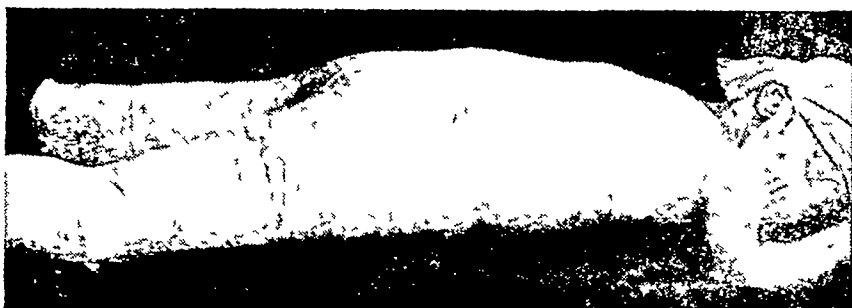
In this series no case of bronchiectasis occurring in the course of a disease of more consequence to the patient than the dilatation itself has been included—thus no bronchiectasis associated with conditions such as carcinoma of the bronchus or the adult form of pulmonary tuberculosis. A review of the ætiological factors concerned is necessary before considering the results obtained in this investigation.

Pneumonia and the Specific Fevers—The commonest antecedent illness from which date a history of symptoms can be obtained is "pneumonia." It has been taught that broncho-pneumonia or lobular pneumonia is more frequent in children than lobar pneumonia, and hence as symptoms most often begin in childhood broncho-pneumonia has been considered the condition from which bronchiectasis most usually develops. However, since radiography has been applied more extensively to respiratory disease, it has become known that non-tuberculous consolidations of lobar extent are not uncommon in children, and that they may pass on to bronchiectasis. Furthermore, collapse of a lobe or lung produces an illness often not differentiated from a true pneumonia, and acute illness diagnosed as pleurisy may well be accompanied by underlying consolidation. These facts make it obvious that an exact division of patients into those whose disease was preceded by broncho-pneumonia, lobar pneumonia or collapse must be very difficult, and in this paper "pneumonia" will be used without further qualification to describe any respiratory illness, the symptoms of which were consistent with the diagnosis of any of the above conditions.

The relationship of pertussis and measles in children and influenza in adults to bronchiectasis is also well known, and adds a further complication—whether these infections of themselves are followed by bronchial dilatation, or whether they merely pave the way for further bacterial invasion and encourage infected collapse due to aspiration. Ramsay and Scadding (1939) drew attention to the fact that such pneumonias may be accompanied by little in the way of symptoms or abnormal physical signs. With regard more particularly to measles, Kohn and Koiransky (1929) in a series of 130 children demonstrated pneumonia radiologically in 62.4 per cent under the age of four and in 42.2 per cent over this age, and often in the absence of signs suggestive of pneumonia. Measles, however, is not a very frequent precursor of bronchiectasis. Pertussis, on the other hand, is regarded as a common cause of the condition (Lander, 1950). Nicholson (1949) observed 44 children, who were sufficiently ill to be admitted to hospital with pertussis, for periods up to one year or until the radiological picture returned to normal. Seven children (15.9 per cent) suffered from collapse which was still present after one year, and hence probably had developed bronchiectasis.

Chronic Respiratory Catarrh—The first respiratory symptoms complained of in a considerable number of patients consist of recurrent bronchitis or "chestiness" since infancy. Very little is known about the ætiology of these cases, but it is doubtful if uncomplicated chronic bronchitis leads to bronchial dilatation. Diamond and Van Loon (1942) did not note that chronic bronchitis in children developed into bronchiectasis although the symptoms of the two diseases were much alike. Most writers have mentioned these factors but with scant comment. An exception must be made in the case of those authors who have judged allergy to be an important antecedent influence in

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bronchiectasis It may be remarked that in the same way as pneumonia is difficult to diagnose, so is uncomplicated bronchitis, and it is a common-place for a clinical diagnosis of bronchitis to be associated with radiographic shadows suggestive of pneumonia

Primary Tuberculosis—It has been known that an enlarged tuberculous lymph gland could compress a bronchus and lead to pulmonary collapse since Gairdner described the association in 1850 at autopsy The conception that bronchial dilatation might follow as a sequel is of relatively recent development although two such cases were reported by Gee in 1877 Brock, Cann and Dickinson (1937) gave particulars of bronchiectasis following obstruction of a bronchus by tuberculous adenitis in several children They stated that "No proven cases observed in childhood have been followed into adolescence or adult life, and the development of true bronchiectasis demonstrated clinically and radiographically" Since this time series have been set forth by Kent (1942), Richards (1944), Graham and Hutchison (1947), Roberts and Blair (1950) and others, drawing attention to this sequel of the primary complex

Mustard Gas—Ever since the 1914-18 World War a proportion of men who were exposed to inhalations of mustard or other vesicant gas, have complained of "bronchitis" and chronic cough Loeper (1919) studied a number of gassed patients at autopsy and found bronchial dilatation present, and Bonnamour, Badolle and Gaillard (1929) confirmed these findings in survivors by means of bronchography Carr, Denman and Skinner (1947) investigated a number of workers who had been exposed to similar fumes by accident during the recent war, bronchograms were done in 144 and bronchiectasis found in 87

Post-Operative Pulmonary Complications—In 1908 Pasteur drew attention to massive collapse following abdominal operations, but Elliott and Dingley (1914) were the first to suggest that such collapse might be caused by blockage of the bronchi due to retained secretions At the present time it is generally believed that retention of secretion acts as the primary factor and that any condition which makes clearing of the air passages difficult, renders atelectasis more likely If the collapse is persistent infection may occur as a complication and bronchiectasis follow Bronchiectasis following tonsillectomy is probably due to the inhalation of septic material

Pulmonary Sequelæ of Irradiation—The literature on intensive irradiation of the thorax often mentions fibrosis of the lung as a sequel, but I have been unable to find any reference to bronchiectasis, although it accompanies pulmonary fibrosis associated with other conditions Huguenin, Lemoine and Fauvet (1947) described a patient who died with symptoms suggesting an infected bronchiectasis following post-radiation pulmonary disease, but unfortunately no post-mortem material was obtained One case occurred in the present series

Pulmonary Infiltrations and Eosinophilia—A chronic type of pulmonary infiltration associated with eosinophilia, and closely related to asthma, was described by Harkavy in 1941 Livingstone (1950)

has described the association of these infiltrations with bronchiectasis, usually patchy in distribution and fuso-saccular in form

Apart from the more obvious causes of bronchiectasis there are certain more general and less clearly related factors which must be considered as having possible significance

Bacteriology—Thorpe (1929) recorded a mixed bacterial flora from 27 specimens of sputum obtained direct at bronchoscopy, and Greey (1932) in 9 lobectomy specimens examined under sterile conditions confirmed these findings. Smith (1927 and 1930), however, found spirochetes and fusiform organisms in the sputum of 49 out of 60 cases of bronchiectasis. He considered that they initiated the disease by destroying the elastic and muscular tissue of the bronchus. Smith and Rusk (1927) on the contrary expressed the opinion of most observers that spirochetes and fusiform bacilli are not primary invaders, but represent secondary infection. Allison, Gordon and Zinnemann (1943) thought that the *hæmophilus influenzae* played an important rôle in bronchiectasis as it was present in the sputum of 65 of the 100 cases which they investigated. Very numerous examinations of the bacterial flora of sputum in patients suffering from bronchiectasis have been made, but the consensus of opinion does not attribute the disease to any specific infective agent

Sinusitis—Sinusitis has been known to be frequently associated with bronchiectasis since Thomson (1914) noted its presence with purulent bronchorrhœa, but agreement has not been reached regarding its significance. It has been proved without doubt that material can be aspirated from the nasal passages into the lungs, and that the aspiration of pus into the bronchi from infected sinuses is extremely probable, but there is no unequivocal evidence that bronchiectasis is caused by the inhalation of septic material from the nares. Clinically, it is known that sinusitis is a very common accompaniment of bronchitis and other acute infections of the respiratory system, as well as bronchiectasis. Walsh and Meyer (1938) investigated 217 patients, excluding cases which had followed the inhalation of a foreign body and also congenital bronchiectasis. They found 145 (66·8 per cent) with evidence of sinusitis. These findings and many others show that those with bronchiectasis have a high incidence of sinusitis, but it should be remembered that chronic sinusitis is far commoner than bronchiectasis, and that the latter is not seen to develop at all frequently in patients suffering from sinusitis. Nor is there any sound evidence to suggest that infection often spreads from the bronchi upwards to the sinuses, although purulent sputum can certainly be coughed into them, an observation easily confirmed by the presence of iodised oil within the sinuses after bronchography

Allergy—Cases of massive atelectasis occurring with asthma have been reported by Kamchorn and Ellis (1921) and Kessel and Hyman (1928), and in children by Peshkin and Fineman (1931). Miller, Piness, Feingold and Friedman (1935) and others have drawn attention to the relatively common occurrence of respiratory disturbances, which

they thought were allergic in origin and not due to infection, in bronchial asthma. They described shadows, both segmental and lobular in distribution, which commonly cleared after the disappearance of the allergic state, but might recur in the same or a different position with a further attack of allergy. There is no doubt that asthmatics are sometimes labelled as suffering from pneumonia or recurrent pneumonia and even pulmonary tuberculosis when the radiological abnormality is primarily due to allergy. Tucker (1931) showed the way in which lobar collapse occurs in asthma by removing the obstructing plug of secretion through a bronchoscope, after which re-expansion took place. The above work has shown that atelectasis can occur and recur in asthma and allergic bronchitis, but has in no way proved that there is any ætiological significance between this disease and bronchiectasis. A definite association between the two conditions is frequently met, but both are common. The majority of authorities have not thought that asthma occurred especially in bronchiectasis. Diamond and Van Loon (1942) found only 4 per cent of their bronchiectatics with asthma whereas it was present in 17.3 per cent of their chronic bronchitics. Waldbott, Kaufman and Merkle (1950) found only four cases of permanent bronchiectasis among 756 patients with chronic asthma, although in nine others they found evidence of reversible bronchiectasis.

Asthma, however, is not the only condition judged to be allergic and criteria have varied considerably as to what may be considered so. Watson and Kibler (1938) believed that 90 per cent of bronchiectasis seen in their area was allergic in origin. They thought that the first stage was "basal allergic bronchitis" which, if untreated, developed into bronchiectasis. In their opinion the allergic swelling of the mucosa and the outpouring of secretion caused collapse. The presence and permanence of bacterial infection determined whether or not bronchiectasis developed. Essentially similar findings were reported by Davison (1944) who judged 80 per cent of 50 bronchiectatics to be allergic. He considered that hypersensitive children who suffered from an acute respiratory infection were more likely to be left with bronchiectasis and sinusitis. His criteria of allergy were the presence of nasal polyps or many eosinophils in the nasal or bronchial exudate. Thomas, Van Ordstrand and Tomlinson (1945) noted a major allergic respiratory condition in nearly half of 190 consecutive bronchiectatics.

These figures for allergy in bronchiectasis are very suggestive but are subject to the same criticisms as those for sinusitis and bronchiectasis. Bronchiectasis is seldom seen to develop in the asthmatic or allergic patient—the association is noticed after the development of ectasis. However, it is likely that this factor has been paid too little attention in the past, and the considerable number of bronchiectatics whose only past abnormality has apparently been chronic respiratory catarrh must be observed. Such symptoms are suggestive of allergy, and the work of Diamond and Van Loon (1942) must be considered in relation to the fact that in 37 per cent of their 75 bronchiectatics

no obvious causal factor was found. It seems certain that much further work must be done upon this group of "chesty" children and also on the considerable group of adults who trace their symptoms to an attack of bronchitis before the factor of allergy can be discounted, but no one has shown by prolonged observation that more of those who suffer from asthma or allergic bronchitis are liable to develop bronchiectasis than the remainder of the population.

Congenital Bronchiectasis—There has been much discussion but no agreement as to the reality of congenital bronchiectasis. It was described as occurring in as many as 10 per cent of 200 cases by Whitwell (1949), Lander (1947) takes the opposite view that this condition does not exist. I have not been able to find any pathological description of congenital bronchiectasis in which the bronchi communicated with the cystic spaces in a foetus which had never breathed, thus undoubtedly proving that the dilatations were not acquired. For these reasons and also because in those cases in this series, which were accompanied by thin-walled "cystic" dilatations and could be placed in this group, a less dubious ætiological factor was present, attention has not been directed to this cause.

MATERIAL AND CRITERIA OF DIAGNOSIS

This survey was conducted over a period of five years (1947-1951) from a chest clinic responsible for a population of about 150,000 centred on Bedford, a county town and urban district of over 60,000 inhabitants which is surrounded by small urban and rural communities. The majority of patients were referred for diagnosis or found in the course of routine radiography, but 21 adults and 5 children were sent up for observation or treatment with the diagnosis already known. One hundred and thirty-seven adults (73 male and 64 female) and 29 children (14 male and 15 female) were collected in whom the dilatation was proved by bronchography. All ages have been calculated from the time of first coming under my care, and those under the age of 15 have been classified as children. A further 48 cases of undoubted bronchiectasis were seen, but as they were not subjected to bronchogram they have been ignored in the detailed analysis. As stated already, bronchiectasis that has followed or accompanied a disease which is of more importance to the patient than the dilatation of the bronchial tubes themselves has not been included, and so no case caused by inhaled foreign bodies, carcinoma of the bronchus, metastatic carcinoma, aneurysm and diseases of such a nature. Post-primary tuberculosis has been most carefully excluded as an ætiological factor. The primary complex of tuberculosis causing pulmonary collapse followed by bronchiectasis has been admitted because it is felt that the dilatation is more important to the patient than the old healed lesion and also because of the known impossibility of exclusion in a small number.

In the past criteria of diagnosis have varied very considerably. For instance, Farrell (1936) diagnosed bronchiectasis on the plain



FIG 1—Right lateral bronchogram on 5 1 51 showing bronchiectasis of the apical segment of the right lower lobe



FIG 2—Antero posterior bronchogram on 4 4 51 showing total bronchiectasis of the right lung and dilatation of the basal branches of the left lower lobe



FIG 3—Postero anterior radiograph on 22 4 49 showing opacities in the right upper and middle zones and increased shadows spreading upwards and outwards from the left hilum



FIG 4—Antero posterior bronchogram on 30 8 50 showing bilateral bronchiectasis of fuso saccular type

radiograph even if iodized oil showed no dilatation, and others have done similarly whenever the alveoli failed to fill with oil Bradshaw, Putney and Clerf (1941), Thomas *et al* (1945) and others have been satisfied with the evidence obtained on bronchoscopic examination Only a few authors, among whom Ogilvie (1941), Evans and Galinsky (1944) and Waldbott *et al* (1950) may be mentioned, have drawn attention to any difficulty in interpreting dilatation on bronchograms In the present investigation some uncertainty in deciding whether true dilatation was present has been experienced in a small proportion

TABLE I

Cases of Bronchiectasis in Adults and Children Analysed According to Primary Ætiological Factors

Ætiological Factor	Adults		Children		Adults and Children	
	No	Per cent	No	Per cent	No	Per cent
Pneumonia	64	46.7	2	6.9	66	39.8
Pneumonia and empyema	5	3.7			5	3.0
Pertussis	5	5.9	5	17.2	13	7.9
Pertussis and pneumonia	3	2.2	2	6.9	5	3.0
Pertussis and measles	1	0.7			1	0.6
Influenza	4	2.9			4	2.4
Measles	1	0.7			1	0.6
Measles and pneumonia	1	0.7	2	6.9	3	1.8
Diphtheria	1	0.7			1	0.6
Scarlet fever with pneumonia	1	0.7			1	0.6
"Black Fever"	1	0.7			1	0.6
Bronchitis	13	9.6	5	17.2	18	10.9
Cough since infancy	12	8.8	5	17.2	17	10.0
Primary tuberculosis	5	3.7	7	24.2	12	7.3
Mustard gas	8	5.9			8	4.9
Post operative chest complications	4	2.9			4	2.4
X radiation to chest	1	0.7			1	0.6
Pulmonary infiltrations with eosinophilia	1	0.7			1	0.6
Pulmonary abscess	1	0.7			1	0.6
Hæmorrhagic disease of the new born			1	3.5	1	0.6
Unknown	2	1.4			2	1.2
Total	137	100.0	29	100.0	166	100.0

No bronchi that have tapered towards the periphery nor any that were partially filled unless grossly dilated have been judged ectatic A number of border-line cases have been omitted, and those included have been viewed by two or more observers all of whom have diagnosed bronchial dilatation independently

ANALYSIS OF ÆTIOLOGICAL FACTORS IN THIS SERIES

The primary ætiological factors found in this survey of 166 patients are presented in detail in Table I Whenever such factors have been complicated by a second disease this has been noted under a separate heading and percentages have been estimated individually These

calculations have been made for adults, children, and the two combined, so that they may be compared with those found elsewhere in various age groups. It must be stressed that although many writers have published figures on the ætiology of bronchiectasis, there is no uniformity in their methods of presentation, and some articles do not state the age groups of those described. There are also large differences in the percentage of cases reported as of unknown ætiology. A further source of error lies in the fact that some series include a small proportion of bronchiectasis following the inhalation of foreign bodies and carcinoma of the bronchus.

Pneumonia —The group of conditions combined under this heading has been found to be the commonest antecedent factor by the majority of investigators. As noted previously it includes pneumonia, bronchopneumonia, pleurisy, empyema and severe respiratory illness. The percentage due to pneumonia in the children (6.9 per cent) is a small one, conversely the percentage found in adults (50.4 per cent) and the two combined (42.8 per cent) is high.

Pertussis —This factor has been mentioned in some series merely as pertussis and in others complicating diseases such as pneumonia or measles have been tabulated in addition. There is a wide variation in these figures. The position occupied by the present series is about the mean, and was 24.1 per cent among the children, 8.8 per cent among the adults and 11.5 per cent over the two combined.

Influenza —This often diagnosed disease has been very variously treated as an ætiological factor, a number of authors have omitted it altogether. In the adults and children combined it was the cause in 2.4 per cent, but it did not appear as a cause among the children. It is possible that these cases might have been better placed under the heading of pneumonia.

Infectious Diseases of Childhood —Measles, diphtheria, scarlet fever and other similar illnesses (excluding pertussis) have been considered under this heading. As ætiological factors they have been described in very varying percentages. In this series measles was judged responsible for 6.9 per cent of the children, diphtheria, scarlet fever and "black fever" for 3.5 per cent of the adults.

Chronic Respiratory Catarrh —Recurrent or chronic bronchitis and cough since infancy have been mentioned as factors by some authors and probably by others have been considered as indefinite or unknown. For example, Walsh and Meyer (1938) classed 47 per cent of their cases as of unknown ætiology and do not mention bronchitis at all, and in children Diamond and Van Loon (1942) placed 37.3 per cent in a similar category. Here they have been divided into two groups —those who have had cough since infancy, and those who have traced their symptoms from recurrent or chronic bronchitis and "chest colds". The percentages found are high and are explained by the fact that whenever this complaint has been reported it has been treated as an ætiological factor and not classed as of unknown ætiology. The two conditions together were responsible

for 34.4 per cent of the children, 18.4 per cent of the adults, and 20.9 per cent of the whole number

Primary Tuberculosis—This was judged to be the cause in 7 (24.2 per cent) of the children, and 5 (3.7 per cent) of the adults, thus making a total of 12 (7.3 per cent) of the whole number. Five of the children were seen at the time of the initial primary lesion, and the process watched from collapse to partial radiological clearing. It is of great interest to note that three of them were left with radiological abnormalities that were in no way typical of healed primary tuberculosis. The other 7 patients had heavy hilar calcifications associated with calcifications of segmental distribution extending into the lung of the typical type left behind by primary tuberculosis.

Mustard Gas—Gassing was the ætiological factor in 8 (5.9 per cent) of the adults. Every one of these patients had been in sufficient contact with mustard gas to need medical treatment, 6 had required admission to hospital. None had complained of any symptoms referable to the chest previously, and all had suffered from cough and sputum gradually increasing in severity from the time of exposure.

Other Causes—Injury to the lung following therapeutic irradiation of the chest is believed to have been the ætiological factor responsible for bronchiectasis in one woman. It has not been possible to find a description of proved bronchiectasis following this cause, and therefore a short history of the case is given.

CASE REPORT 10657—A married woman aged 39 had her right breast removed for carcinoma in May 1948. Before this she had suffered from no serious illness nor had she had any symptoms referable to her lungs. A radiograph on 10th June 1948 showed no abnormality in the lung fields. She was irradiated daily from 10th June to 16th June 1948. The skin dosage was 2814 R and the tumour dosage 2500 R applied to the chest wall and axilla. Cough and sputum developed after this treatment, and a radiograph taken on 21st August 1948 showed bilateral abnormal shadows suggesting irradiation pulmonary disease. A further film on 5th November 1948 showed considerable extension of the shadows on the right side with shift of the heart to the right, and slight diminution in the shadows on the left side. Spontaneous fractures had also occurred in the 7th and 10th right ribs. By July 1949 the patient was in very poor health with œdema of the ankles, free fluid in the abdomen and an enlarged liver, she was thought to have developed secondary deposits. However, during the next six months she improved, all evidence of œdema disappeared and her complaints were limited to cough, sputum and general asthenia. First seen on 5th January 1950 she was very thin, and the right hemithorax was much reduced in size, deeply pigmented anteriorly and presented physical signs typical of total collapse. There was clubbing of the fingers, but no evidence of secondary deposits was found. A radiograph taken on 13th January 1950 showed atelectasis of the right lung, and some thickening and crowding of the pulmonary markings over the lower zone of the left lung. The heart was displaced to the right and an ununited fracture of the 7th right rib was present. Her erythrocyte sedimentation rate was 68 mm at one hour (Westergren) and the sputum was negative for tubercle bacilli. A bronchogram performed on 4th April 1950 showed bilateral

bronchiectasis (Fig 2) Her condition remained little changed until April 1951 when she died suddenly, still with no evidence of secondary deposits

Recurrent pulmonary infiltrations with eosinophilia were present in one patient associated with bronchial dilatation As few cases of this syndrome have been described brief details are appended

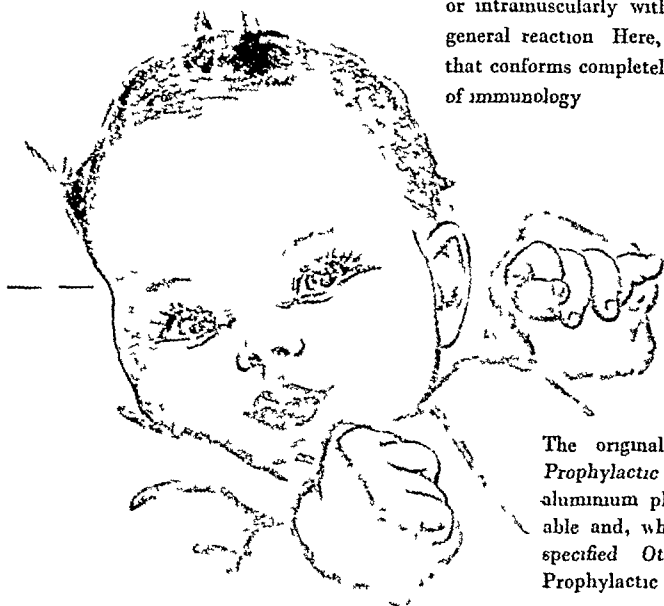
CASE REPORT 10659—A male aged 30 was first seen on 9th January 1950 during an acute respiratory illness The patient gave a history of asthma, frequent in childhood, but much less so of recent years For some years he had had bronchitis at intervals of a few months with normal health and no chest symptoms in between A radiograph on 12th January 1950 showed a small area of shadowing in the right upper zone and a few "ring" shadows in the middle zone, and extensive shadowing in the left upper and middle zones with numerous "ring" shadows The general picture suggested pulmonary tuberculosis or possibly pneumonia The sputum was repeatedly negative for tubercle bacilli, but unfortunately no blood count was done Shortly afterwards two previous X-ray films became available, the first of which had been taken in August 1948 and disclosed opacities of indefinite shape over both upper and middle zones, the second taken in April 1949 (Fig 3) showed a similar type of shadowing though of different distribution After viewing these radiographs it became obvious that an unusual condition was present, and serial radiographs showed that the shadowing on the left side was diminishing but that new shadows were appearing on the right side By June 1950 there was a small area of infiltration on the right side with a few "ring" shadows in the middle zone and on the left there were much more marked "ring" shadows in the upper and middle zones with a little irregular infiltration On 14th September 1950 he reported again having had an attack of asthma about 14 days previously The X-ray film was little changed, but a white cell count showed 9000 leucocytes per c mm, 14 per cent being eosinophils A bronchogram on 30th September 1950 (Fig 4) revealed bilateral bronchiectasis

Pulmonary abscess has figured in most series as an ætiological factor It may be difficult to tell whether this is a primary condition causing bronchiectasis or whether it arises secondary to long-standing disease In my series only one patient was judged as having developed bronchiectasis in the area occupied by a pulmonary abscess which was known to have arisen in a previously normal lung One other case came under observation for a pulmonary abscess, but this was thought to be a complication as it occurred in the only normal segment of a bronchiectatic lung in a patient with a long history of symptoms One child had suffered from hæmorrhagic disease of the newborn, and was believed to have inhaled vomited blood, he had coughed since infancy In two patients no ætiological factor could be discovered, one was referred because of dyspnœa on exertion, and one, a Pole, was unable to give any lucid account of himself

Associated Diseases—Sinusitis was present in 48.2 per cent of the children, in 28.4 per cent of the adults, and in 31.9 per cent of the combined groups In the main only patients who had suggestive symptoms or signs of sinusitis were investigated for its presence, and doubtless this accounts for the low overall percentage found The figure for children reflects the fact that the majority were sent to the special department for opinion, but also a far higher proportion had

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symptoms referable to the area Asthma was present in 5·4 per cent. of the total

CORRELATION OF ÆTIOLOGICAL FACTORS AND OTHER ASPECTS

Age of Onset—Most authorities have found that about half their patients dated the onset of symptoms to the first decade of life, and in this series 73 out of the 154 with symptoms fell into this group. When the ætiological factors are analysed this is seen to be largely dependent on the fact that many of the illnesses concerned are only common under the age of 10. Pertussis, the infectious fevers, and cough since infancy are obvious examples, and primary tuberculosis seldom gives rise to lymphadenopathy sufficient to cause bronchial obstruction except in children. In every decade pneumonia proved to be the most frequent cause. In the first decade it accounted for 31·2 per cent, and by the third decade pneumonia and recurrent bronchitis were the only two factors of consequence remaining. In spite of the early age of onset of symptoms the largest number (42 or 25·3 per cent) came under observation during the fourth decade.

Duration of Symptoms—The average length of time that symptoms had been present before the patient came under observation was 17·3 years, and is longer than that which has been reported previously. Riggins (1943) gave an estimated duration of 16·4 years, Clark, Hadley and Chaplin (1894) 11·8 years, Ogilvie (1941) 11 years, and Warner (1935) 10 years. The individual duration of symptoms varied from two weeks to 48 years, but in only 17 patients was over 34 years. Over this range cases were distributed evenly, and it was the same with all the main ætiological factors except primary tuberculosis in which the interval was only 2·7 years, due to 5 of the 12 cases coming under observation as contacts, and 4 having no symptoms.

Presence of Symptoms—It would be of interest to know if bronchiectasis due to various ætiological factors was of more or less severe type. For this reason the symptoms commonly found in this disease are tabulated in Table II, and the percentage suffering from individual symptoms and signs related to each ætiological factor. The descriptive terms used require clarification. Thus by constant cough and sputum it is meant that cough and sputum were present regularly every day. Hæmoptysis is self-descriptive, and the term "stained sputum" indicates that small quantities of blood mixed with sputum had been coughed up on one or more occasions but that as much as one teaspoonful of blood had never been reported. Patients were described as having constant abnormal physical signs if such were present whenever examination was made. Clubbing of the fingers was used to define all degrees of this condition from the earliest stages which have been well described by Branwood (1949) to the most advanced. Primary tuberculosis was associated with a smaller incidence of symptoms and abnormal physical signs than any other condition. There was little difference between the other antecedent factors, after allowance is made for small numbers.

Number and Extent of Lobes Affected—The average number of lobes affected with bronchiectasis was 2.6 throughout the whole series, but when primary tuberculosis was the ætiological factor it was only 1.1 lobes. The extent of the disease in a lobe was also much less following this cause. In the whole series there were 32 patients in whom the total area affected with bronchiectasis was less than that of the smallest lobe (right middle lobe). Of the 12 post-tuberculous cases 7 (58.3 per cent) were of this type, which will be termed segmental in this paper. No other factor was responsible for anything like so high an incidence of segmental bronchiectasis.

TABLE II

The Number of Cases of Bronchiectasis due to Various Ætiological Factors together with the Percentages in each Group having Certain Symptoms and Signs

Factor	Total No of Cases	Percentage with Symptoms of					
		Constant Cough	Constant Sputum	Hæmo- ptysis (not less than ½ oz)	Stained Sputum	Constant Abn Phys Signs in Chest	Clubbing of Fingers
Pneumonia	71	84.5	80.2	25.3	23.9	73.2	50.7
Pertussis	20	90.0	70.0	20.0	25.0	75.0	35.0
Influenza	4	100.0	100.0	25.0	25.0	50.0	25.0
Infectious diseases of children	6	100.0	100.0	16.6	33.3	100.0	66.6
Bronchitis	18	66.6	66.6	16.6	27.7	72.1	44.4
Cough since infancy	17	94.1	88.2	23.5	29.4	94.1	52.9
Primary T B	12	41.6	25.0	25.0	25.0	25.0	8.3
Mustard gas	8	75.0	75.0	12.5	50.0	100.0	75.0
Post operative chest	4	75.0	75.0	50.0	25.0	100.0	25.0
Various	4	75.0	75.0	50.0	50.0	75.0	50.0
Unknown	2	50.0	50.0		50.0	50.0	
All causes	166	80.7	73.4	20.4	27.7	74.1	45.1

Recurrent Pneumonia—A patient has been assessed as suffering from recurrent pneumonia if it occurred in addition to the initial illness. Fletcher (1935) found that 28 per cent of his patients had been affected in this way, and Perry and King (1940) reported 24 per cent. In this series 40.4 per cent suffered from one or more attacks. It was found most likely to arise if the initial ætiological factor was pneumonia. Primary tuberculosis, on the other hand, was followed by pneumonia on only one occasion.

DISCUSSION

No apology is needed for emphasising the importance of the ætiological factors leading to disease. Until they are known prevention, so much to be preferred to the alleviation of symptoms or even cure, is difficult or impossible. This survey has shown that patients with bronchiectasis may be divided into two main classes: those in whom

the origin of their illness is known with reasonable certainty, and those where the cause must be adjudged as doubtful or unknown. The first group, whose symptoms follow definite illnesses such as pertussis or primary tuberculosis, can to some extent be avoided by a variety of prophylactic measures. When pneumonia is already present the need for energetic treatment is well understood and probably effective in reducing the incidence of bronchiectasis, although it may be that a number of severe cases develop bronchiectasis instead of dying. The second group, which has been variously treated as of unknown ætiology or arising from recurrent bronchitis or cough since infancy, thus assumes a particular importance as further progress in prevention must await a surer ætiological background. Two alternative theories of causation have been held responsible. A considerable body of opinion believes that allergy is the main factor and that satisfactory treatment for this state would reduce the incidence of subsequent bronchiectasis. Whether allergy is primarily responsible as was thought by Watson and Kibler (1938) and others, or whether it merely renders a concurrent acute respiratory infection more likely to cause bronchiectasis (Davison, 1944) is not certain. However, many have been struck by the large number of chronic asthmatics and bronchitics who do not suffer from bronchial dilatation and question whether it is commoner among them than the remainder of the population. Those who do not believe that allergy is important consider that superadded pneumonia is responsible for the onset of bronchiectasis in the large majority. They point to the difficulty of diagnosing pneumonia without adequate radiological control, and argue that there may be no severe symptoms even if infected collapse follows. No definite conclusion can be reached regarding the ætiology of this group, but radiography, if employed at each exacerbation over long periods, should help to provide an answer.

A comparison of the ætiological factors found in the present series with those in others, shows certain differences, most of which are probably explained by variation in the methods of classification and the source of material. These reasons can hardly account for the high percentage caused by primary tuberculosis (7.3), and mustard gas (4.9) in a general series of bronchiectatics. The former is only mentioned as an ætiological factor by Raia (1938), and only isolated cases due to the latter have been recorded. It is difficult to understand why they have received so little attention, particularly primary tuberculosis which, noting its frequency (24.2 per cent) among the children, must be a common cause among the older age groups. The explanation that these patients as children are usually segregated among the tuberculous is valid, but does not explain their absence from surveys of adults, unless they have been deliberately excluded without mention or their ætiology has ceased to be obvious. In favour of the last solution is the observation drawn from this series—that half the children seen to develop bronchiectasis following primary tuberculosis failed, within a few years, to show specific evidence of

their ætiology One case each of bronchiectasis following post-radiation pulmonary disease and pulmonary infiltration with eosinophilia were described Neither cause has figured in previous series of bronchiectatics, although they probably will do so in the future, as neither syndrome is rare On the negative side no case was found to follow tonsillectomy

It has not been possible to find a review relating the extent and symptoms of bronchiectasis to the relevant ætiological factors Any such analysis would only be of significant value if large numbers were collected in order that the rarer causes could be compared with the common ones Impressions, however, can be obtained from relatively small series, and in bronchiectasis such impressions have been responsible for building up the sum of knowledge which we have to-day The relation of ætiological factors to the age of onset of symptoms shows that those with bronchiectasis may be divided into two broad groups the first occurring before the age of 10 in which the majority are due to the infectious diseases of childhood, cough since infancy, and primary tuberculosis, the second arising after the age of 10 which is largely caused by pneumonia, chronic bronchitis and various other conditions, many of which belong to the miscellany of aspiration pneumonia The age of coming under observation and the duration of symptoms were much the same whatever the ætiology The actual duration of symptoms (17.3 years) was longer than the average reported This may be accounted for, in part by the fact that the severer examples tend to drift to the large hospitals from which most series have been compiled, and also that a considerable proportion of the cases of bronchiectasis in this area are either small in extent or not suffering from marked symptoms The symptoms found varied little whatever the ætiology except with primary tuberculosis, but following this condition they were less marked in every category chosen Moreover, when the number of lobes affected was compared, it was discovered that far fewer lobes were affected in the cases due to primary tuberculosis, and also that the extent of the damage was much less One of the most troublesome complications of bronchiectasis is recurrent pneumonia and before the advent of chemotherapy and the antibiotics the most frequent cause of death (Perry and King, 1940, Bradshaw *et al*, 1941) When this was related to the ætiological factors it was found to occur more commonly (63.4 per cent) in those who traced their symptoms to pneumonia than any other condition It is interesting to note that primary tuberculosis was followed by pneumonia in only one patient

From the above findings it might appear that bronchiectasis following primary tuberculosis is more benign than when it follows other diseases, but it must be remembered that this disease is usually responsible for small areas of bronchial dilatation only Moreover, partial stenosis of a bronchus, likely to cause some difficulty in drainage, is common in this type of bronchiectasis and rarely associated with the others under consideration For this reason it might be expected

that certain complications would be more probable, and indeed have been described by Brock (1950). I think that its apparent benignity in this series is due to the small areas affected rather than to any other reason. Most observers have thought that the symptoms caused and the prognosis of bronchiectasis depended particularly upon its extent, though Raia (1938) pointed out that there is a trend to mildness or severity which becomes apparent early in the course of the disease, an observation that may well depend upon the type of inflammatory reaction between the bronchi. This trend appears to be mild after primary tuberculosis.

I am deeply indebted to Dr F. P. Lee Lander without whose encouragement this investigation would never have been started, and to Dr Neville C. Oswald for his help in preparing the paper. My thanks are due to Mr G. Kent Harrison in whose department some of the bronchograms were done, to Dr J. H. L. Easton, Physician to the Bedford General Hospital, and to the many general practitioners of the area for their help in referring patients for investigation. I am also indebted to Dr E. N. Moyes who performed many of the bronchograms, and to Dr W. C. V. Brothwood, County Medical Officer for Bedfordshire for his co-operation.

SUMMARY

(1) A short historical review of some of the factors concerned in the causation of bronchiectasis has been made.

(2) During a period of five years all cases of bronchiectasis ascertainable within an area of nearly 150,000 people have been collected together. One hundred and sixty-six (137 adults and 29 children) were confirmed by bronchograms, a further 48 cases were diagnosed but not proved by bronchograms, and therefore not included in the detailed analysis.

(3) Bronchiectasis followed pneumonia in 50.4 per cent of the adults and 6.9 per cent of the children. In comparison with other series these were respectively the highest and lowest figures found.

(5) Chronic respiratory catarrh was the only reported abnormality in the history of 20.9 per cent, it was therefore classed as an ætiological factor. The relationship of this group to allergy and pneumonia has been discussed.

(6) The percentages due to primary tuberculosis (7.3) and mustard gas (5.9) were higher than those previously reported. One case followed post-radiation pulmonary disease and one case was associated with pulmonary infiltrations and eosinophilia.

(7) The ætiological factors found were correlated with age of onset, age of coming under observation, duration of symptoms, certain symptoms and signs, number of lobes affected, segmental bronchiectasis, and recurrent pneumonia.

(8) Onset in the first decade was associated particularly with the infectious diseases of childhood, primary tuberculosis and cough since infancy, and in the following decades with pneumonia and recurrent bronchitis.

(9) Little difference was found in the type of bronchiectasis following the various ætiological factors except for primary tuberculosis, which was followed by fewer symptoms and signs, a smaller number of lobes affected, and a higher percentage of segmental bronchiectasis

(10) Recurrent pneumonia occurred most often when pneumonia was the antecedent factor, it arose once only in bronchiectasis following primary tuberculosis

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CAROTID SINUS SYNDROME AND CAROTID BODY TUMOUR

By W MICHIE, M B, F R C S (Edin), and R G SIMPSON, M D,
M R C P (Lond)

Aberdeen General Hospitals

THE following case is of interest in that it illustrates the characteristic manifestations of the carotid sinus syndrome. Unusual features are the co-existence of a carotid body tumour and the prompt and complete relief of all symptoms following surgical removal of the tumour.

CASE REPORT

A lady now aged 47 started seven years ago to suffer from transient mental "blackouts," *i.e.* attacks of clouding of consciousness, during which she felt dizzy and faint. The attacks recurred three or four times a month, often around the time of menstruation. She was invariably standing or sitting when the attacks occurred, and she observed that they were often precipitated by sudden movements of the head—such as stretching up to a high shelf in her draper's shop. During the late summer of 1950 the "blackouts" became progressively more frequent, and, up to the time of her admission to hospital in January 1951, there were numerous episodes daily—often twenty or more, scarcely a day passing without incident. Throughout the course of the illness there were a dozen or more occasions when the clouding of the sensorium rapidly gave way to loss of consciousness, she would fall to the ground, usually lying pale and motionless for $\frac{1}{2}$ -2 minutes, but in four instances, repetitive clonic movements of arms and legs were noted by witnesses. Her general health had always been good, apart from sore throats for many years. After an attack of tonsillitis fifteen years ago, she noticed a swelling in the right side of the neck, below the angle of the lower jaw, this had persisted, showing little variation in size, and had never been painful or tender.

Family history disclosed no important information.

On examination she was found to be a stout cheerful person and a good witness. The temperature was 98.6° F, the pulse rate 98 per minute, and the B P 170/90 mm Hg. The mouth and throat were healthy. A firm, discrete and lobulated mass of walnut size was visible and palpable just below the angle of the mandible on the right side (Fig 1). It was not tender, the overlying skin was normal, and the mass was freely movable only from side to side and not vertically. The heart was normal. Detailed examination of the nervous system did not disclose any important abnormalities. The urine contained neither albumin nor sugar. Hb 95 per cent (Haldane). The blood Wassermann reaction was negative. Spinal fluid showed normal pressure, cell-count and protein content, and a negative Wassermann reaction. A radiogram of the chest and an electrocardiogram were normal.

INVESTIGATIONS

The close proximity of the swelling in the neck to the carotid sinus suggested the possibility of the patient's symptoms being those of the

carotid sinus syndrome, while the mass itself seemed to display the essential clinical characteristics of a carotid body tumour. While the patient was lying in bed, firm pressure with the thumb on the tumour caused a dramatic response: there was an almost immediate increase in the rate and depth of the respirations, succeeded in a few seconds by an abrupt and profound fall of the blood pressure and heart rate, followed by a prolonged period of cardiac standstill. Unconsciousness supervened seven seconds after the onset of the reaction, and persisted for as long as compression was maintained. Release of digital pressure at

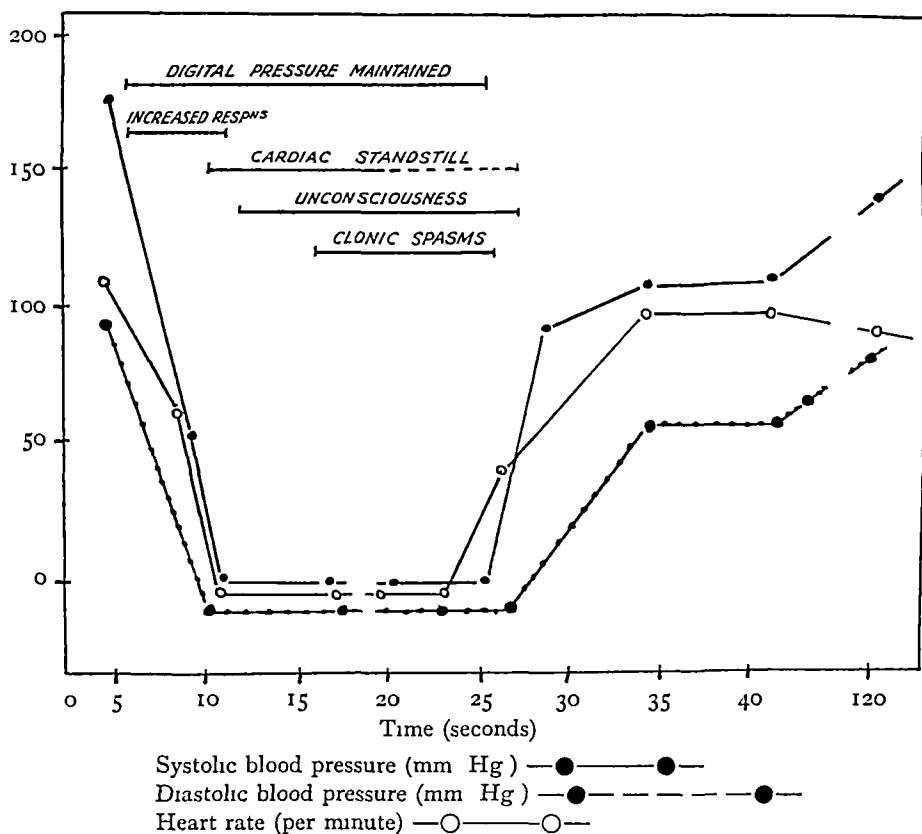


Fig 2 —Diagram showing effects of digital pressure on hypersensitive carotid sinus

the end of twenty seconds was followed by a prompt return of consciousness together with a gradual restoration of the heart rate and blood pressure to their former levels. Pressure on the left carotid sinus caused only slight and temporary slowing of the heart rate and no impairment of consciousness. Adequate digital compression on the right side never failed to reproduce this response, the clinical observations being supplemented by continuous electrocardiographic recordings on a direct-writing machine. The findings are briefly presented in Figs 2 and 3. All of the deliberately induced reactions were essentially identical, and the subjective sensations noticed by the patient both before and after the periods of syncope were the same as those which she had experienced with her spontaneous attacks. Since the tumour



FIG 1 —Showing swelling due to carotid body tumour below angle of jaw on right side

was so situated as to cause pressure on a highly sensitive carotid sinus, it seemed reasonable to expect that surgical removal of the tumour might at least diminish the distressing frequency of the spontaneous attacks. In order to explore the possible effects of handling the tumour at operation, digital compression was carried out during a trial period of deep general anaesthesia with thiopentone, nitrous oxide, oxygen and ether. A continuous cardiogram showed a slight degree of slowing and irregularity of the heart's action and there was no significant fall in the blood pressure.

OPERATION

Deep anaesthesia was induced by the agents previously employed. Since the tumour was relatively small and well defined, a generous skin crease incision was used in preference to one along the anterior border of the sternomastoid. Following the division of platysma and deep fascia the sternomastoid was retracted backwards and the tumour mass, enveloped by the carotid sheath, was exposed over its entire extent.

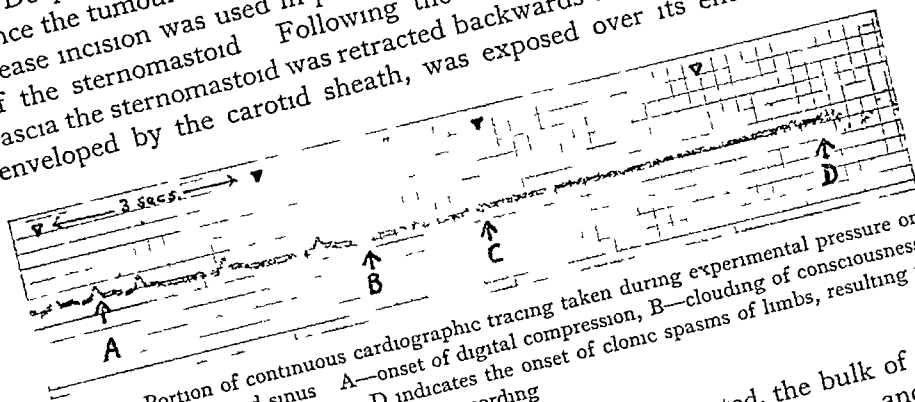


Fig 3—Portion of continuous cardiographic tracing taken during experimental pressure on the right carotid sinus. A—onset of digital compression, B—clouding of consciousness, C—loss of consciousness, D indicates the onset of clonic spasms of limbs, resulting in interference with the cardiographic recording.

Though the carotid vessels were partially incorporated, the bulk of the tumour lay anteriorly and medially. Vascularity was extreme, and as bleeding came mainly from surface oozing, control was limited to swab pressure. The main blood-supply derived from the carotid bifurcation and only after the tumour had been dissected free from its attachment to the bifurcation was hæmorrhage completely controlled. The internal jugular vein was stretched across the tumour, but was freed by sharp dissection. The sympathetic trunk and the vagus and hypoglossal nerves were similarly exposed and preserved.

No unusual alterations in respiratory or cardiac function were noted during the operation or in the post-operative period, and subsequent convalescence was uneventful. The patient has remained symptom-free since the time of operation. On six separate occasions—pressure on the right and left carotid sinuses separately has failed to produce any significant alterations in respiration, heart rate, blood pressure, cardiographic record, or the state of consciousness.

The Pathological Report on the tumour was as follows—"Macroscopically this specimen appears as a brownish-yellow lobulated and

apparently well encapsulated tumour measuring $5.4 \times 3.4 \times 2$ cms. On one surface the tumour shows a deep Y-shaped groove presumably due to its close relationship to the bifurcation of the common carotid artery. The specimen has been bisected and the cut surface is of a fairly uniform greyish-yellow colour intersected by a few irregular greyish coloured, hyaline fibrous bands (Fig. 4). Microscopically (Fig. 5) the tumour is seen to have a 'peritheliomatous' pattern—consisting of small clumps of large polyhedral cells, often showing an indistinct outline, with a vacuolated eosinophilic cytoplasm and a large vesicular nucleus usually containing one or more nucleoli and a coarse chromatin network. Many of these clumps of cells surround thin-walled vascular sinuses and are themselves separated from each other by compressed vascular spaces lined by endothelial cells. There are extensive wide bands of hyaline fibrous tissue and a few focal deposits of hæmosiderin pigment are noted. It is considered that this is a carotid body tumour which is histologically benign."

DISCUSSION

The Carotid Sinus Syndrome—This condition was first fully described as a clinical entity in 1933 by Weiss and Baker, further papers by Weiss and his associates have dealt exhaustively with the clinical aspects of the subject (Ferris *et al*, 1935, and Weiss *et al*, 1936). Since the condition has received comparatively little attention in British literature, it may be useful to give a brief account here of its main features.

The essential characteristics of the syndrome are recurring attacks of disordered consciousness almost always associated with transient and profound alterations of the heart rate and blood pressure, the manifestations are those of an exaggerated carotid sinus reflex which is presumed to arise from abnormally sensitive pressure-receptors in the wall of the carotid sinus. The present case is a typical example of the remarkably uniform clinical picture seen with this condition. It is most common over the age of 45 and tends to affect men more often than women. Many of the subjects have signs of arteriosclerosis or hypertension, and the oversensitive sinus can often be palpated because of dilation or local sclerosis, but in a small minority of cases there may be a localised swelling in the neck, most often caused by clinically enlarged lymph nodes, in close relation to the sinus. The attacks of impaired consciousness, which usually last for $\frac{1}{2}$ -3 minutes, are sometimes initiated by sudden movements of the head or by pressure on the neck, such as may be caused by a tight collar, but frequently such exciting factors are not evident. However, digital compression of the oversensitive carotid sinus will almost always confirm the diagnosis by precipitating an attack.

Both conservative and surgical methods of treatment are available. General measures include the avoidance of sudden head movements

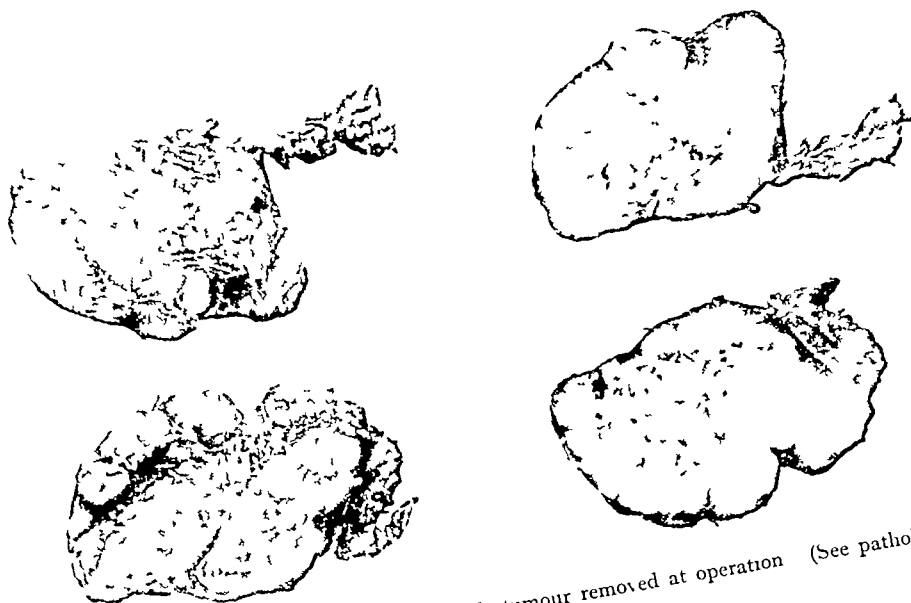


FIG 4—Gross specimen of carotid body tumour removed at operation (See pathological report in text)

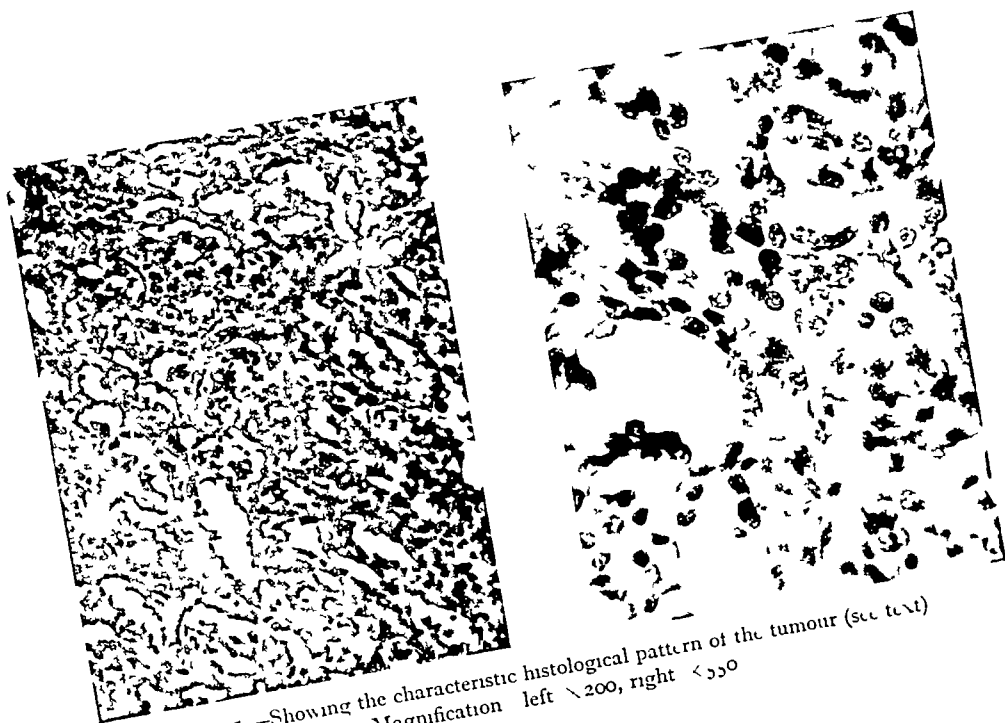


FIG 5—Showing the characteristic histological pattern of the tumour (see text)
Magnification left $\times 200$, right $\times 550$

and of tight neckwear. In most instances the frequency and severity of the attacks can be diminished or the attacks prevented by the oral use of certain drugs, of which ephedrine hydrochloride $\frac{1}{2}$ grain (0.03 gm) t d s, atropine sulphate 1/120 grain (0.0005 gm) t d s, or tincture of belladonna 15 minims (1 ml) t d s, seem to be the most effective. The results of deep X-ray therapy applied to the carotid sinus have not been encouraging. Where conservative measures fail to reduce the frequency of attacks, surgical treatment may have to be considered. The most effective procedure appears to be surgical denervation of the carotid sinus, which is effected by "stripping" of the sinus and of the common, internal and external carotid arteries for a short distance below and above the sinus, the intercarotid tissue, including the carotid sinus nerve, is also freed and divided.

Carotid Body Tumour—There have in all been approximately 300 cases recorded, and the literature has already been adequately reviewed by several authors (Gordon-Taylor, 1940, Lahey and Warren, 1947, 1951, Le Compte, 1948, and Monro, 1950), but the present case is especially worthy of note because the patient suffered from attacks of carotid sinus syncope consequent upon the presence of the tumour. This has been reported previously in only three instances, and since the association of syncope with tumour is so uncommon, it would appear that the tumour itself does not play a primary role in the production of syncopal attacks but acts probably by pressing on a hypersensitive carotid sinus. The relief of symptoms following removal of the tumour in the present case can probably be attributed mainly to denervation of the sinus caused by stripping of the carotid vessels and of the tissues in the carotid bifurcation during the operation.

In conclusion it is suggested that the carotid sinus pressure test may be usefully included in the clinical investigations of those patients who present with a history of recurring mental "blackouts". The test is simple to perform and gives as a rule reliable results, and although it is rarely attended by undesirable effects, caution must be observed with elderly persons in whom unduly prolonged digital pressure should be avoided. In these individuals compression should be released promptly on the development of unconsciousness or cardiac standstill, and it is wise to have at hand a syringe containing 8 minims (0.5 ml) liquor adrenaline hydrochloride which may be given subcutaneously should recovery be delayed. Adrenaline has been shown by Weiss *et al* (1936) to be capable of aborting most attacks of carotid sinus syncope.

SUMMARY

An example of the carotid sinus syndrome in a patient with carotid body tumour is described.

Prolonged remission of symptoms has followed surgical removal of the carotid body tumour.

The general features of the syndrome are briefly reviewed

The results of various investigations suggest that the symptoms in the present case were caused by pressure of the tumour on an over-sensitive carotid sinus

We wish to thank Dr C D Needham for permission to publish this case and for his helpful criticism For the pathological report and photographs, we are indebted to Dr Douglas Scott of the Department of Pathology, University of Aberdeen

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NOTES

At the Quarterly Meeting of the College held on Tuesday, 22nd July 1952, the President, Dr W A Alexander, in the Chair, the following were elected Fellows — Daw Yin May, M R C S ENG, L R C P LOND, F R C S E, Maung Shwe Zan, M B EDIN, William John Gibson Barrie, M B E, M D EDIN, James Wright Rae, M B EDIN

The following were elected Members of the College — Anthony Flavien Stanislaus Perera, L M S CEYLON, Mohd Ayub Khan, M B PUNJAB, Walter Sneddon Watson, M D EDIN, William Jonathan Abel, M B EDIN, Nimal Krishna Mitra, M B CALC, Andrew Bogdan, M D LOND, Geoffrey Hugh Templeman, M B E, M D LEEDS, Arthur Jarrett, M B BIRM, Matthew Walter John Boyd, M D BELF, Newton Symonds Chalk, M B QUEENSLAND, Pathiyil Karthiyayam Krishnankutti, M D MADRAS, Sureshwar Prazad Jha, M D PATNA, John Buller Cromie, M D BELF, Henry Gemmell Morgan, M B ST AND, Charles Desmond Ross Pengelly, M B BRISTOL, Harry Altman, M B WITWATERSRAND, Eveline Patricia Forbes, M B CAPE TOWN, Leo Schamroth, M B WITWATERSRAND, Lionel Hugh Mofflin, M B ADELAIDE, Peter George Aungle, M B EDIN, Janet Latta Picken Hunter, M B GLASC

At a meeting of the Royal College of Surgeons of Edinburgh held on 21st July 1952, Professor Walter Mercer, President, in the Chair, the following who passed the requisite examinations were admitted Fellows — Victor Paul Amato, M D UNIV MALTA, 1943, Manulal Purshottam Amin, M B, B S UNIV BOMB 1945, Hilla Banaji, M B, B S UNIV BOMB 1945, M D UNIV BOMB 1948, Amar Chand Bhandhela, M B, B S UNIV PUNJAB, 1944, Pesi Behramshaw Bharucha, M D UNIV BOMB 1947, James Alexander Lamb Clark, M B, CH B UNIV EDIN 1941, Colin James Ross Conacher, M B, B S UNIV SYDNEY, 1944, Rosemary Helen MacNaughton Davie, M B, CH B UNIV EDIN 1948, Frederick John Guzar, M B, CH B UNIV NEW ZEAL 1943, Ahmed Adly Hammouda, M B, CH B UNIV CAIRO, 1942, Joseph Moise Mayer, M B, CH B UNIV BAGHDAD, 1944, M R C S ENG, L R C P LOND 1950, Alan Hector Garson Munro, M B, B S UNIV DURHAM, 1935, Nanalal Ranchhodji Petel, M B, B S UNIV BOMB 1943, Arthur Douglas Roy, M B, CH B UNIV GLASC 1947, Max Schaffer, M B, CH B UNIV CAPE TOWN, 1938, William Seright, M B, CH B UNIV GLASC 1946, Bertram Leslie Shaff, M B, B CH UNIV WITWATERSRAND, 1946, Abdel Hamid Shouman, L R C P & S EDIN (TRIPLE) 1942, Ellis Martin Sparrow, M B, CH B UNIV CAPE TOWN, 1944, Kenneth Sutherland Stewart, L R C P & S EDIN (TRIPLE) 1944, John Geoffrey Stonham, M B, B S UNIV MELB 1928, M D MELB 1931, Willoughby Wilson, M B, B CH QUEEN'S UNIV BELFAST, 1946

FELLOWS IN DENTAL SURGERY

The following candidates having passed the requisite examinations were admitted Fellows in Dental Surgery — David William Dick, L D S, R F P S GLASC 1941, H D D, R F P S GLASC 1950, John Aird Russell, L D S, R F P S GLASC 1944, H D D, R F P S GLASC 1948

At a Graduation Ceremonial held in the McEwan Hall on Wednesday, 16th

University of
Edinburgh

July 1952, the following degrees were conferred —

The Degree of Doctor of Medicine—Marion Bowie Bethune, Scotland, M B, CH B (WITH HONS), 1938 (*Highly Commended for Thesis*), John Cecil Cruickshank, Scotland, M B, CH B, 1921 (*Awarded Medal for Thesis*), John Walter Adam Duckworth, England, M B, CH B, 1936 (*Awarded Medal for Thesis*), Robert Alexander Kemp Harper, Scotland, M B, CH B, 1929, Runa Blyth Mackay, Scotland, M B, CH B, 1944, Alan Ramsey Muir, England, M B, CH B (WITH HONS), 1947 (*Highly Commended for Thesis*), Thakur Ram Nath Parhar, India, M B, CH B, 1935, Colin Heriot Macdonald Walker, Scotland, M B, CH B, 1946

The Degree of Doctor of Philosophy—*In the Faculty of Medicine*—Bruce Cruickshank, M B, CH B, Zbigniew Godlowski, M D (CRACOW), M R C P (ED), Ronald Haxton Girdwood, M B, CH B (WITH HONS), F R C P (ED), M R C P (LOND), Autar Singh Pantal, M B, B S, M D (LUCKNOW), Lilli Stein, M A (CANTAB)

The Degrees of Bachelor of Medicine and Bachelor of Surgery—David Hume Adamson, Scotland, James Charles Aickin, New Zealand, John Alexander Aitken, Scotland, Norman Colvin Allan, Scotland, Harry Cochrane Allen, England, Anne Johnston Anderson, Scotland, Andrew Armstrong, Scotland, Evan Francis Auden, Jamaica, Timothy Awuku-Asabre, Gold Coast, William McAlpine Ayles, Scotland, John Alexander MacDonald Bain, Scotland, Arthur Banks, England, Frank Macrae Begg, Scotland, William Duncan Bennett, Scotland, Alastair James Berry, Scotland, Hugh Sharp Polson Binnie, Scotland, Sheila Hamilton Birse, Scotland, Gerald Claverton Biss, England, Alexander Bisset, Scotland, Allan Black, Scotland, James George Blyth, Scotland, Heather Bremner, Scotland, Alison Grace Hilda Brown, Scotland, Jean Forbes Brown, Scotland, Donald Budge, Scotland, Douglas Cadger, Scotland, Helen Maclean Caldwell, Scotland, Hamish Argyll Campbell, South Africa, David Ian Bell Carrie, Scotland, Thomas Meredith Chalmers, Scotland, Dennis Gerard Chambers, England, Agnes Clark, Scotland, Henry Grosvenor Clarke, B SC (LOND), England, Allan Craig, Scotland, Margaret Cramb, Scotland, Findlay McDonald Robertson Cranston, Scotland, George Alexander Graham Crease, Scotland, Samuel Howard Davies, England, Kenneth John Dennis, Scotland, Margaret McCombie Dewar, Scotland, Agnes Mam Dickson, Scotland, Andrew Doig, Scotland, Peter Holt Dootson, England, Betty Duncan, Scotland, James Kelman Edwards, Scotland, William Alexander Elliott, Scotland, Edward Thomas Faunch, England, William Ferguson, Scotland, John Alistair Duncan Gilhes, Scotland, Joyce Yvonne Graham, Scotland, Robert William Graham, Scotland, Michael John Grayson, England, William Moncrieff Hanning, Scotland, Daphne Veronica Marjorie Halliday, Scotland, William Harrison, Scotland, Pamela Percival Hartley, England, George Izatt Hendry, Scotland, Rena Elizabeth Hogg, Scotland, James Hood, Scotland, Margaret Hope, Scotland, Agnes Campbell Howie, Scotland, Constance Catherine Mary Howie, Scotland, George Anthony Ives, England, Thomas Peter Carlton Jameson, England, Victor Walker Johnston, England, Septimus Matthys Joubert, M SC (STELLENBOSCH), South Africa, Lilius Kilpatrick, Scotland, Christine Catherine Graham Krause, Scotland, Mairi Hodgkinson Lack, Scotland, John Patrick Laidlaw, Scotland, Richard Baillie Laidlaw,

Scotland, Ann Leslie Langley, England, Adam William Blyth Lawson, Scotland, William Joseph Hannay Leckie, Scotland, Peter Brotherston Lesslie, Scotland, Charles Donald Livingstone, Scotland, Margaret Allison Lorane, B SC, Scotland, Ian Alexander Lowe, Scotland, George Ballantyne McAulay, Scotland, Hugh Fraser MacConnachie, Scotland, Alexander McDonald, Scotland, Hamish John McDonald, Scotland, Hugh Macdonald, Scotland, Isobel Macdonald, Scotland, Jean Murray Macdonald, Scotland, Robert Macdonald, Scotland, Gerald Patrick McGovern, Scotland, David Paterson McGowran, Scotland, Duncan MacGregor, Scotland, Kathleen Leshe MacGregor, Scotland, George Meiklejohn McLaren, Scotland, John Macleod, Scotland, Murdo Macleod, Scotland, Inez Melrose McMurray, Scotland, John McNae, Scotland, Ian Simpson McRobbie, Scotland, Ronald Gibson Mahaffy, Scotland, John Mein Main, Scotland, John Edward Malcolm, Scotland, Charles Matheson Manson, Scotland, Thomas Williamson Manson, Scotland, Frederick Peter Sefton Marriott, England, John Archibald King Meikle, Scotland, Keith Thomas Wyndham Miller, B SC, Scotland, William Howell Morgan, Wales, James Kinnear Morrison, B SC, Scotland, Norman McQueen Munnoch, Scotland, Dorothy Murphy, Scotland, Peter James Brodie Murray, Scotland, Gerald John Matthewson Nairn, New Zealand, William Jeffrey Newlands, Scotland, Paulette O'Dowda, England, James Noel Park, M A, Scotland, Morag (*nee* MacQuarrie) Parnell, Scotland, Richard Albert Parry, England, Alan Bernard Partridge, M A (CANTAB), England, Margaret Dewar Paton, Scotland, Ronald William Fordyce Paul, Scotland, William Frederick Paveley, England, William Peter, Scotland, Renos Charalambous Phellas, Cyprus, David Edward Baden Powell, Wales, Harry William Singer Rankin, Scotland, Jean McKay Reid, Scotland, Kathleen Mary Robb, Scotland, Michael Kefford Robinson, England, Andrew Isdale Ross, Scotland, Ian Alexander Bruce Mackenzie Ross, B A (CANTAB), Scotland, Thomas Allan Sanderson, Scotland, Peter Dodge Sears, England, Marjorie Elizabeth Joan Shafto, Scotland, Doreen Walker Shennan, Scotland, John Patrickson Shutt, England, Basil Crandles Smith Slater, Scotland, William Denney Smith, Scotland, Alastair Kenneth Morrison Stewart, Scotland, Frederick Lindsay Sturrock, Scotland, James Herkes Tait, Scotland, David Ernest Meguyer Taylor, England, Joseph Arthur Taylor, England, Ian Moyes Thom, Scotland, Colin Hugh Thomson, Scotland, Edward David Macrae Tod, England, Ian Carnochan Kerr Tough, B SC, Scotland, George Henry Wallace, Scotland, George Scott Wallace, Scotland, Alexander Watt, Scotland, Gilbert Owen Way, England, David Bamford Williamson, England, John Boyd Williamson, D S C, Scotland, Alan Oliver Arneil Wilson, Scotland, James Wilson, Scotland, Henry William Wright, Scotland

Diploma in Public Health—Edwin Crighton Byrom Bramwell, M B, CH B, Isobel Beatrice Craighead, M B, CH B, James Drummond, M B, CH B, Robert Reid Gillies, M B, CH B, Robert Stevenson Hardie, M B, CH B, Margaret Graham Martin, M B, CH B, Elizabeth Christina Nelson, M B, CH B, John Hunter Nicolson, M B, CH B, Robert Park, M R C S (ENG), L R C P (LOND), Dattatraya Krishava Ramadwar, M B, B S (CALCUTTA), Shafiqur Rehman, M B, B S (PUNJAB), William Serle, M B, CH B, Charles William Shearer, M B, CH B, Claud Edmund George Wickham, M B, B S (LOND), Ian Macaulay Wood, M B, CH B, Harold William Woolner,

L R C P (ED), L R C S (ED), L R F P AND S (GLASG), Eric Walter Wright, M B, CH B

Diploma in Tropical Medicine and Hygiene—Ahmad Mohamed Ishak El Haddad, M B, CH B (CAIRO), Duncan Murray Cameron, M B, CH B, Duncan Gordon Conacher, M B, CH B, Aisha Zakī Shafel Hanno, M B, CH B (ALEXANDRIA), William Kofie Lutterodt, M B, CH B, Yahia Marzouk, L R C P (ED), L R C S (ED), L R F P AND S (GLASG), Hareebun Bunsee Singh, L R C P (ED), L R C S (ED), L R F P AND S (GLASG), Chengleput Harikrishnan Sivaraman, M B, B S (MADRAS)

Diploma in Psychiatry—Beatrice Margaret Allen, M B, CH B, David Satya Nand, M B, B S (LAHORE)

Sister-Tutor Certificate—Rosanna Cunningham, Dora Helen Marguerite Bailey, Hilda Baker, Jean Mima Barr, Agnes Walker Macdonald Boag, Kathleen Brennan, Olga Helen Brunton, Catherine Nicoll Dallas, Mary Josephine Doherty, Erica Dorothy Garner, Joseph Green, William Arthur James, Douglas McArdle, Frank Finlay Maconaghie, William McGrath, Mary Maciver, Dorothy Marsden, Nora Marsh, Jessie Monteath, Margaret Barr Muir, Nora Pillion, Agnes Vallance Rae, Mary Rankin, Hilda May Saunders, Martha Granger Shout, Kathleen Jean Wallace Wilson

Certificate in Medical Illustration—Sheila Yzetta Calvert Mackie

Awards of Scholarships, Bursaries, Prizes, etc—*The Cameron Prize in Practical Therapeutics*—Karl Paul Link, PH D, Professor of Biochemistry in the University of Wisconsin, in recognition of his work on anti-coagulant therapy *The Ettles Scholarship and Leslie Medal*—Samuel Howard Davies, M B, CH B

The Scottish Association for Medical Education of Women Prize—

Alison Grace Hilda Brown, M B, CH B *The Dorothy Giffillan Memorial Prize*—Alison Grace Hilda Brown, M B, CH B

The Stark Scholarship in Clinical Medicine—John Patrick Laidlaw, M B, CH B

The James Scott Scholarship in Obstetrics and Gynaecology—James Kinnear Morrison, B SC, M B, CH B

The Buchanan Scholarship in Obstetrics and Gynaecology—Samuel Howard Davies, M B, CH B

The Mouat Scholarship in the Practice of Physic—Samuel Howard Davies, M B, CH B

The Beane Prize in Anatomy and Surgery—Samuel Howard Davies, M B, CH B

The Gunning Victoria Jubilee Prize in Anatomy—Alan Ramsay Muir, M D

The Lawson Gifford Prize in Obstetrics and Gynaecology—David Ernest Meguyer Taylor, M B, CH B

The Keith Memorial Prize in Systematic Surgery—David Ernest Meguyer Taylor, M B, CH B

The Conan Doyle Prize—Septimus Matthys Joubert, M SC (STELLENBOSCH), M B, CH B

The Wightman Prize in Clinical Medicine—Marjorie Elizabeth Joan Shafto, M B, CH B

The Annandale Medal in Clinical Surgery—Pamela Percival Hartley, M B, CH B

The Royal Victoria Hospital Tuberculosis Trust Medal—Samuel Howard Davies, M B, CH B

The Murdoch Brown Medal in Clinical Medicine—John Patrick Laidlaw, M B, CH B

The Colonel Thomas Biggam Memorial Medal and Prize in Pathology—James Syme

The George Guthrie Research Fellowship in Child Health—Thomas Theodore Scott Ingram, M B, CH B

The Freeland Barbour Fellowship—Rachel Brodie Mackay, M B, CH B

The Ethicon Research Fellowship—Sarashi Ranjan Mukherjee, M B, B S (CALCUTTA)

The Whaitt Research Scholarship—Henry Bruce Torrance, M B, CH B

The Paterson Travelling Scholarship in Surgery—Hugh Arnold Freeman Dudley, M B, CH B

The Wilkie Surgical Research Scholarship—Edmund Joseph Delorme, M D (TORONTO)

The Crichton Research Scholarship—Rachel Brodie Mackay,

M B , CH B *The Wellcome Medal and Prize in the History of Medicine*—George Dick Forwell, M B , CH B *The Ellis Prize in Physiology*—Krechmir Krnjevitich, M B , CH B , B SC

An Address to the new Graduates was delivered by the Promoter, Professor George Hector Percival, M D , PH D , F R C P (ED)

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh The following passed the Final Examinations, and were granted the diploma of L R C P EDIN , L R C S EDIN , L R F P AND S GLASG —Ranjit Singh Ahluwalia Mavis Fay Anderson, Frederick Jacobus Badenhorst, James Brown Barnett Baird, Carl Edgar Barth, George Alan Christie Binnie, Edwin Henry Brown, Dennis Gerard Chambers, Brian Cornes, William Armstrong Dalglish, Eric Albert Ehlinger, Sydney Fogel, Brenda Gale, Colina Graham, Ruth Esther Graham-Yooll, Jean Marie Henri Roland Hardy, Arthur Rowland Isaac, Amirah Husein Kassam, Viljoen Kritzinger, Claude Hamilton Lalgee, Pamela May Lambden, Peter Angus Lowe, William Allan Mahon, Pearl Kallman Malasky, Christine Wallace Mann, Robert William Stuart Miller, Eric Campbell Moffat, James Ian Morrison, John Aikman McIlvride, Agnes Forrest Mackay, Arbold Orwin, Joyce Elizabeth Anne Ovens, Hedwig Marianne Martha Papigay, Audrey Pilbeam, Jean Margaret Price, Raymond Alfred William Ratchiff, Margaret Helen Rodger, Enid Sagar, Ralph Shabetai, Thelma Dorothy Standing, Robert Steele, Alexander Stevenson, Cyril Ward, Martin Herbert Weinberg, Milton Meyer Weiner

Triple
Qualification
Board

NEW BOOKS

Diseases in Old Age—A Clinical and Pathological Study of 7941 Individuals Over 61 Years of Age By ROBERT T MONROE, M D Pp xi+407 London Geoffrey Cumberlege 1952 Price 32s 6d net

The increasing proportion of old people in the population has opened up a whole new field both in medicine and social medicine In this book the author has surveyed the clinical, pathological and therapeutic material from 7941 elderly persons admitted to the Peter Brent Brigham Hospital The diseases of each system are analysed completely and are summarised at the end of each chapter This work is a very good attempt to establish a basis for geriatrics as a definite and separate branch of medicine The book should be read by all those interested in this subject

The Management of Bronchial Asthma By HERBERT G J HERXHEIMER, M D Pp viii+107, with 16 illustrations London Butterworth 1952 Price 22s 6d net

Dr Herxheimer has written an individualistic and up-to-date review of a subject on which he is an acknowledged authority On drug treatment he presents new ideas which, although they may not receive universal approval, merit further investigation and clinical trial He believes that the anti-histamine drugs, in selected cases, are more useful than is generally recognised Acquired tolerance to adrenaline, ephedrine and similar drugs, and methods of dosage designed to avoid it, are discussed in detail This review, unlike most on the same subject, strikes a note of therapeutic optimism which should prove refreshing to consultant and general practitioner alike

Modern Practice in Tuberculosis Edited by T HOLMES SELLORS, M A , D M , M CH , F R C S , and J L LIVINGSTONE, M D , F R C P Volume I, pp xxviii+355, with 105 illustrations Volume II, pp vii+441, with 161 illustrations London Butterworth 1952 Price £7, 7s

In 29 chapters, written by 39 experts, these volumes cover the morbidity and mortality statistics of tuberculosis, pathogenesis, morbid anatomy, practical bacteriology, B C G , social problems, the psychology of the tuberculous, and clinical and therapeutic aspects of pulmonary tuberculosis There are also chapters on tuberculosis of the lymph glands, abdominal organs, bones and joints, central nervous system, pericardium, skin, eye, and genito urinary system, besides an article on sarcoidosis Most of the contributors come from the United Kingdom and on the whole the book reflects current British thought Anyone interested in tuberculosis will read the book with pleasure and there will be few who do not learn a great deal from it The standard of production is high, the illustrations are clear and, considering the number of authors, it is remarkable how consistently readable are their contributions

The different contributors have attacked their tasks in varying manners Many have done original work in the particular subject they write about and some of these give undue weight to their own views to the exclusion of opposing argument But their views are always worth close attention and on the whole there is far more fact and far less vague opinion in these volumes than in many similar works Among a number of outstanding contributions, Dr Cruickshank's chapter on the quantitative bacteriology of sputum conversion, Dr Clegg's on morbid anatomy, Dr Tattersall's on chest clinics, Dr Richards' on tracheo-bronchial tuberculosis and Sir Hugh Cairns and Dr Honor Smith's on tuberculous meningitis are particularly noteworthy It is perhaps a pity that there is no chapter on methods of research in tuberculosis, a subject to which the British school has made notable contributions, but in general it is difficult to quarrel with this outstanding book

The Life and Work of Astley Cooper By R C BROCK Pp 176, with 14 illustrations Edinburgh E & S Livingstone 1952 Price 20s

Every reader of this excellent biography will agree that the time had come for a reassessment of Astley Cooper's achievement in the world of surgery Since Bransby Cooper published the two-volume life of his uncle, in 1843, little has been done to honour the memory of the great surgeon who was so worthy a successor to John Hunter The son of a clergyman of Norfolk, Astley Cooper became a student at Guy's and St Thomas's Hospitals, then closely linked, and he lived in the house of Mr Henry Cline, whose surgical teaching was an important influence in his life Another influential teacher was Alexander Monro (secundus), under whom Cooper studied during seven months' residence at Edinburgh, and to whom he later dedicated his treatise on Hernia, in 1807 Astley Cooper was already well known as anatomist and surgeon when he was appointed Surgeon to Guy's Hospital in 1800 His skill as an operator, combined with his immense energy and industry, soon carried him to the peak of success as the leading surgeon of his day As might be expected, some of the stories which lend such colour to the previous biography are repeated in this smaller book episodes of the faithful though mercenary butler " Charles," of the dissection of an elephant in the courtyard of Cooper's house, of the removal of a sebaceous cyst from the head of George IV—a risky proceeding in the pre-antiseptic days A full account is given of Astley Cooper's pioneer work in arterial surgery, including his ligation of the aorta It is interesting to note that in 1817 he tied the femoral artery, using a catgut ligature, cutting the ends short, and closing the wound, which healed by first intention This was fifty years before the time of Lister, who is usually regarded as the first to use catgut as a ligature Lister made its use safe, but Astley Cooper was first to use it The writer has done well to recall the work of one who did much to advance the science of surgery and to carry on the Hunterian tradition It is a book which every medical man should read

Fœtal and Neonatal Pathology By J EDGAR MORISON 1952 Pp vi+366, with 59 illustrations London Butterworth Price 50s

This is an important contribution to a subject on which there has been for long need of a modern book. The emphasis is on those factors that may affect the developing fœtus and the ability of the newborn infant to adapt itself to postnatal life. The author believes that advance in knowledge must be made by research in these fundamental aspects of fœtal pathology, rather than by studies based on routine autopsies, and the discussion of the present state of knowledge in this respect is illuminating and excellently done. He has rendered a useful service in his lucid and readable review of many confused and controversial aspects of fœtal and neonatal physiology, in their bearing upon the development of pathological states. The section on infection is also useful and informative. The least satisfactory feature is the actual description of pathological processes. These are often sketchy, and not adequately illustrated. This decreases the value of the book as a work of reference for the use of a pathologist finding his way in this, to many, unfamiliar field of pathology, and seeking guidance in the carrying out of his routine autopsies. The bibliography is large and well chosen.

A New Outlook on Mental Diseases By F A PICKWORTH, M B, B S, M R C S, L R C P Pp 304, with 24 plates, 4 illustrations Bristol John Wright Price 60s net

The book, written by a pathologist, is a tribute to the work and enthusiasm of Dr T C Graves, Birmingham, who concerned himself so greatly with the investigation and treatment of chronic sepsis in all types of mental disorder.

Dr Pickworth has formulated his own views on the basis of his pathological work and has suggested that a proper understanding of the mind and its disorders can only be determined by a disturbance of the vascular system due to chronic toxic infective conditions. He attempts to defend and substantiate this position by his own work and by numerous uncritical quotations from the work of others. Dr Pickworth brushes aside the possibility of any other approach to the understanding of these most complex disturbances. His book, therefore, is an example of biased pleading and dogmatic assertion to a degree that is almost embarrassing. He so simplifies the issues as to make his position untenable.

Under these circumstances it is impossible to recommend this book as a guide or stimulus either to medical students or to the trained psychiatrist.

The Apologie and Treatise of Ambroise Pare, containing the Voyage made into Divers Places, with many of his Works upon Surgery Edited by GEOFFREY KEYNES Pp 227, with four full-page illustrations and a number of woodcuts London Falcon Educational Books Price 15s

Among the medical classics of early times which may still be read with pleasure and profit none ranks higher than the *Works of Ambroise Pare*. What Vesalius accomplished for anatomy, what Harvey did for physiology, Pare set forth in the field of surgery, and became one of the greatest surgeons of all time. His graphic account of his campaigning days is a joy to read, so full is it of action, adventure and humour. To have it now presented in so handy, clear and inexpensive a form is a great advantage, and the sponsorship of so eminent a bibliographer as Mr Geoffrey Keynes is in itself a guarantee of excellence. The second half of the book is devoted to selections from the surgical writings of the master, dealing with hernia, with "wounds made by gunshot, other fierce engines, and all sorts of weapons," with mummie as a remedy, with amputations and fractures and cataract, with cutting for the stone, and the use of bezoar, and finally to end the fine collection, an essay on "How to make reports," from which even the modern recorder may glean some helpful advice. The volume is illustrated by four full page portraits of Pare, and by a selection of the original woodcuts. This well timed reproduction of a classic may be cordially recommended, not only to the surgeon and medical student, but also to the general reader who will find in it a vivid picture of a stirring time.

NEW EDITION

The Rhesus Factor By G FULTON ROBERTS, M A, M D Third Edition Pp vii+90
London William Heinemann 1952 Price 5s net

First appearing in 1947 this little book is now in its seventh printing—evidence of its popularity and usefulness This new edition, still intended as a brief and elementary survey, has been increased by the addition of two new chapters and by short notes on other blood groups It has been thoroughly brought up to date and should be of the greatest assistance to the clinician in dealing with hæmolytic disease

BOOKS RECEIVED

- BAILEY, HAMILTON, F R C S (ENG), F A C S, F I C S, F R S E, and LOVE, R J
MCNEILL, M S (LOND), F R C S (ENG), F A C S, F I C S A Short Practice
of Surgery Ninth Edition (*H K Lewis & Co Ltd, London*) 55s net
- BROTHERSTON, J H F, M A, M D, D P H Observations on the Early Public
Health Movement in Scotland (*H K Lewis & Co Ltd, London*) 21s net
- CLAYTON, E B, M B, B CH (CANTAB) Electrotherapy and Actinotherapy
Second Edition (*Bailliere, Tindall & Cox, London*) 16s net
- COLLINS, VINCENT J, M D Principles and Practice of Anesthesiology
(*Henry Kimpton, London*) 75 net
- DECKER, ALBERT, M D, D O G, F A C S Culdoscopy
(*IV B Saunders Company Ltd, London*) 17s 6d
- GARDNER, ERNEST, M D Fundamentals of Neurology Second Edition
(*IV B Saunders Company Ltd, London*) 24s
- Edited by HEWITT, RICHARD M Collected Papers of the Mayo Clinic and the
Mayo Foundation Volume XLIII
(*IV B Saunders Company Ltd, London*) 60s net
- JOHNSON, JULIAN, M D, D S C (MED), and KIRBY, CHARLES K, M D A Hand
book of Operative Surgery of the Chest
(*The Year Book Publishers Inc, Chicago*) 68s
- KEMP, TAGE, M D Genetics and Disease (*Oliver & Boyd Ltd, Edinburgh*) 60s net
- LAKE, NORMAN C, M D, M S, D S C (LOND), F R C S (ENG) The Foot
Fourth Edition (*Bailliere, Tindall & Cox, London*) 25s net
- Edited by LANSING, ALBERT I, PH D Cowdry's Problems of Ageing Third
Edition (*Bailliere, Tindall & Cox, London*) 114s net
- LEOPOLD, SIMON S, M D The Principles and Methods of Physical Diagnosis
(*IV B Saunders Company Ltd, London*) 37s 6d
- MONCRIEFF, ALAN, M D, F R C P, and THOMSON, WILLIAM A R, M D Child
Health Second Edition (*Eyre & Spottiswoode, London*) 21s net
- MUNRO, DONALD, M D, F A C S Injuries to the Nervous System
(*IV B Saunders Company Ltd, London*) 37s 6d
- PUNT, NORMAN A The Singer's and Actor's Throat
(*William Heinemann, London*) 10s net
- RITVO, MAY, M D, and SHAUFFER, I A, M D Gastrointestinal X Ray Diagnosis
(*Henry Kimpton, London*) £7, 10s net
- SHAFFER, CARL F, M D, F A C P, and DON, W CHAPMAN Correlative
Cardiology (*IV B Saunders Company Ltd, London*) 47s 6d net
- Edited by WOLSTENHOLME, G E W, O B E, M A, M B, B CH Ciba Founda
tion Colloquia on Endocrinology Volume II
(*J & A Churchill Ltd, London*) 35s net
- WRIGHT, SAMSON, M D, F R C P Applied Physiology Ninth Edition
(*Oxford University Press, London*) 50s net
- Advances in Medicine and Surgery from the Graduate School of Medicine of
the University of Pennsylvania (*IV B Saunders Ltd, London*) 40s net

Edinburgh Medical Journal

October 1952

THE RETICULOSES AND LYMPHORETICULAR SARCOMAS FROM THE RADIOTHERAPIST'S POINT OF VIEW

By MARGARET C TOD

WHEN I took the reticuloses as my subject I found that if I were to make the best use of the material provided by the case records of the Christie Hospital it would be necessary to include a large group of anaplastic radiosensitive tumours which are not true reticuloses but sarcomas or even, possibly, carcinomas. I also decided that it would be most useful if I gave most of my time to the commoner conditions and refrained from descriptions of single cases however rare and unusual. It was tempting to study the strange forms taken by some of these hyperplasias of lymphoreticular tissues, their spectacular complications such as skin lesions, their rapid progress and even, occasionally, their unexpected cure, but each case is almost unique and experience with one gives little help for the next. I am a radiotherapist with treatment my main concern, and the results of treatment can only be assessed if numbers are available which allow statistical evaluation. For this, wide grouping is needed, and that which I shall suggest is used to try to find out how present methods of treatment can most usefully be applied.

Reticulosis is a name applied to certain forms of neoplasia which appear to be multifocal in origin and have characteristic symptoms of systemic disturbance. When the true sarcomas of lymphoid tissue are included, whether they be differentiated or anaplastic, the term lymphoreticular neoplasia is more accurate. For purposes of this discussion I have regarded the following pathological reports as indicating the presence of a reticulosis or lymphoreticular neoplasm, Hodgkin's disease or lymphadenoma, Brill-Symmer's disease or lymphoid follicular reticulosis, leukæmia, lymphosarcoma, reticulum cell sarcoma, anaplastic sarcoma, and cases with such doubtful reports as "anaplastic tumour, may be either sarcoma or carcinoma." This list is incomplete but it follows my declared intention to deal only with common conditions.

PATHOLOGY

There is no group of diseases about which more uncertainty exists. Their ætiology, their nature and their manifestations are all subjects of dispute, and the difficulty of making a definite diagnosis from

histological material obtained by biopsy is well known. During the last 30 years there have been a series of phases which might be described as changes of fashion in nomenclature. At one time the theory that all the conditions here described as reticulosis were infective granulomas held the field, and the word sarcoma was seldom used. Next the pendulum swung back to the idea of neoplasia and many cases of Hodgkin's disease which had become malignant were called polymorphic or reticulum cell sarcoma. Then came the classification by Robb Smith, excellent in that it drew attention to how the cells grow in the affected nodes, but too elaborate for every day use and now seldom seen in the reports we receive. Finally, during the last few years there has been a return to the use of names, and we have Hodgkin's disease, Brill-Symmer's disease, Schuller-Christian disease and the Letterer-Siwe syndrome. Often the report on the named disease is qualified by saying that it is atypical or by phrases implying uncertainty or offering a choice of diagnosis. A new difficulty has also arisen regarding the true nature of some anaplastic tumours, and cases with multiple enlarged lymph nodes, showing all the clinical signs we associate with reticulosis, may be reported as anaplastic or even as transitional cell carcinoma secondary to an unknown primary.

My own belief, and that on which we base our concept of these diseases, is that they form one continuous spectrum of neoplasia on which stand out peaks consisting of tumours of distinct recognisable character. The theory that all these tumours form one spectrum is related to their common origin in the primitive mesenchyme, the provider of the stem cells for all differentiated lymphoreticular tissue. This follows the teaching of Dawson, Innes and Harvey¹ of the Edinburgh school, who speak of "The stem cell of lymphoid tissue having *in situ* the productive potentialities of endothelioblast, fibroblast and lymphoblast". Clearly such a cell could give rise to tumours differing greatly in appearance but of similar basic character. Willis² also accepts this theory of origin and writes of "The chaos of names which has developed in the attempt to identify and separate the neoplasms of lymphoid tissue when all are only variants with many transition forms and capable of being changed from one to another". He allows that certain types, Hodgkin's disease, reticulum cell sarcoma or Brill-Symmer's disease are sufficiently differentiated to show definite character. He stresses, however, the importance of the completely undifferentiated tumour and says, "A completely anaplastic sarcoma is indistinguishable by microscopic study alone from any other completely anaplastic growth".

Here is a border line where confusion between sarcoma and carcinoma certainly occurs. This adds to the difficulty of some radiotherapists who have come to attach great importance to the differing sensitivity of mesodermal and epidermal tumours and expect the pathologist to distinguish between them. On this point Willis says, "I repeat my conviction that excluding tumours sufficiently differen-

tiated for positive histological identification there is no type of structure alleged to be characteristic of any form of sarcoma or endothelioma which may not be perfectly imitated by areas of atypical carcinoma " Writing of this lack of distinction in their discussion of lymphoepithelioma Harvey, Dawson and Innes,³ after mentioning the points by which carcinoma might be separated from sarcoma say, " Neither architecture nor cytology is sufficiently distinctive " and conclude that many so-called lympho-epitheliomas are actually reticulum cell sarcomas If this is true, it must be a waste of time to try to separate the anaplastic tumours, but positive identification, when possible, remains of great importance, and the presence of this intermediate zone of indeterminate tumours does not excuse lack of knowledge of the changes which follow differentiation either towards true connective tissue sarcoma or to the familiar epidermoid carcinoma

To allow the argument to be continued it will be taken as agreed that the spectrum consists of various forms of neoplasia of the primitive mesenchyme, some of which are indistinguishable from undifferentiated tumours of immature epithelial character, and of some growths sufficiently differentiated to have characters easily recognised in histological section Outstanding among these conditions is the familiar Hodgkin's disease, but Brill-Symmer's disease also has an individual appearance Both of these conditions are true reticuloses in the sense that they appear as systemic diseases affecting the lymphoreticular tissues, but can be equally correctly described as tumours of the primitive mesenchyme A third reticulosis which has recently been described in detail is the lipoid reticular form with three variants, eosinophil granuloma, Schuller-Christian disease and the Letterer Siwe syndrome A few cases of this reticulosis have been treated by us but not enough for separate classification and useful comment This may not be the last of the reticuloses to be distinguished, but if new forms await discovery they must be very rare.

My second main group includes all the lymphoreticular sarcomas and anaplastic tumours because I believe that, although lymphosarcoma and reticulum cell sarcoma are sufficiently differentiated to be recognised, they merge imperceptibly into the anaplastic tumours Outside our spectrum but very close to it come the cancers described as anaplastic, lympho-epithelioma and transitional cell carcinoma, none of which can be excluded when the anaplastic sarcomas are studied It may seem that all this discussion has merely separated out Hodgkin's disease, a highly individual condition often diagnosed by clinical examination, and leaves all the other lymphoreticular tumours in a state of complete confusion There is confusion, but that is why it is necessary to search for facts on which treatment may be based, and I believe that when the analysis of our findings has been followed it will be agreed that this simple division into two groups allows treatment to be determined

The acceptance of the theory of mesenchymal origin does not

solve all the problems of the diagnosis and treatment of these puzzling diseases. There are some strange anomalies in their behaviour, and they have not yet been satisfactorily separated from the infective granulomas. There is, for instance, continuing confusion about the nature of the condition known as sarcoidosis. Thanks to the work of Cameron and Dawson we now recognise this as a form of tuberculosis, but in the U S A it is often described as if it were a true neoplasm. There are considerable differences between the work published abroad and that published in this country, and it sometimes seems that the same name is not given to the same disease.

MATERIAL

The material available for analysis is provided by the cases treated at the Christie Hospital, Manchester, during the eight years 1940 to 1947 on a diagnosis of "reticulo-endothelial neoplasia," a term adopted by us in 1937 and much used by radiotherapists but unpopular with pathologists, who now replace it by lymphoreticular neoplasia. Nearly 900 cases were so listed, but of these I have discarded —

- 1 Sixteen bone tumours (Ewing's tumours and multiple myelomatosis)
- 2 Thirteen cases of polycythæmia (number too small for analysis)
- 3 Ninety-four cases classed as reticulo-endothelial neoplasia but lacking definite pathological report

I was tempted to use those cases without pathological report which followed a characteristic clinical course but decided against this in case they might invalidate my comparisons. The cases to be analysed, 777 in all, were without exception proved by pathological examination of sections. The diagnosis was not always immediate, but the case records were often in themselves complete confirmation of a report which had expressed some doubt. Sometimes clinical findings alone were enough, but further biopsies were often taken, sometimes before instituting further treatment or because response was unexpected. There were also a number of autopsies.

The method of taking the biopsy is important. The small amount of tissue made available by aspiration or even by the new drill biopsy instruments is inadequate for the diagnosis of these border-line conditions. If possible a whole lymph node should be excised or, in cases where the nodes are fixed in a large mass of tumour, a substantial piece should be taken. On the other hand we have found that attempt at complete excision, except in really early cases where block dissection could be carried out, was followed by early and widespread metastases. Good biopsies having been available, it is possible to claim that the classification now to be given is based on pathology, and even a report of anaplastic tumour was acceptable, particularly as it was often possible

to get an expression of opinion regarding probable origin by discussing the case with the reporting pathologist

The cases are grouped as follows —

Hodgkin's disease	275 cases
Brill-Symmer's diseases	24 „
Lymphosarcoma	108 cases
Reticulum cell sarcoma	57 „
Anaplastic tumours, may be either sarcoma or carcinoma	156 „
The leukæmias	157 „

The two conditions which may be regarded as true reticulosis have been grouped together because of the similarity of their multifocal lymphadenopathy and systemic symptoms. Both must be regarded as almost incurable although their course may be long, sometimes lasting for years, the long duration showing as five-year survivals in the tables of results. Occasionally an early case radically treated either by surgery or by irradiation seems to be cured, but this is rare because, even if the treated lesion remains well, new manifestations finally appear, although they may take forms so unexpected that they are not at first recognised. Hodgkin's disease is the commonest of all these neoplasias, and its histology has often been described. Jackson⁴ and Parker have published a detailed study in which they subdivide into three groups Hodgkin's paraganuloma, Hodgkin's granuloma, and Hodgkin's sarcoma. Their description is that the paraganuloma is found in lymph nodes with lymphocytes as the predominant cell, although Reed-Sternberg cells are found on searching. There are transition forms to the granuloma which is usually widespread and characterised by the presence of many Reed-Sternberg cells and by pleomorphism. The sarcoma usually originates in the intra- or retro-peritoneal lymph nodes or abdominal organs and behaves as a malignant infiltrating tumour. The diagnosis of Hodgkin's disease is established by the presence of Reed-Sternberg cells. It has not been possible to divide the Manchester material into these three types. There have been a number of cases diagnosed as "early Hodgkin's" which fit with the histological picture of the paraganuloma, but the diagnosis is made on small nodes removed for biopsy, and such a report may be received even when there are advanced lesions elsewhere in the body. Nor has it been possible to distinguish sarcomas of the type they describe. There have been true sarcomas infiltrating outside the capsule of the lymph nodes and producing secondary deposits in lung, liver or bone, but they have not been common within the abdomen. In general, the only consistent histological difference we have found to distinguish early and late cases has been the number of mitoses indicating rate of growth. The points on which the diagnosis rests are the characteristic Reed-Sternberg cells, the endothelial reaction, the position of the cells in the medulla and the presence of eosinophils, fibrosis and necrosis.

Clinical characters are a low average age incidence, preponderance of males and a comparatively long duration before the need for treatment is realised. This is probably because the first sign is nearly always painless enlargement of lymph nodes causing no inconvenience. Hodgkin's disease is essentially a neoplasm of lymph nodes which, unless sarcoma supervenes, remain freely mobile and have a characteristic rubbery feel. Systemic complications, fever, itching of the skin and anæmia are common and may lead to profound cachexia and death. The other cause of death is the appearance of sarcomatous infiltration and metastatic deposits. The nature of this sarcomatous change is interesting and it is used as an argument in favour of true neoplasia against the theory of a specific infection. On the other hand, it is important that this is the only disease in this series which consistently shows a response to treatment by nitrogen mustard. There is, of course, an effect in the blood diseases, but this is due to the generalised action of these drugs on the hæmopoietic system. In Hodgkin's disease it has a specific effect which we have not seen in Brill-Symmer's, or any of

FIG A1 —Lymph node showing typical Hodgkin's disease

FIG A2 —The same to show Reed Sternberg cells

FIG A3 —Histological picture in Brill Symmer's disease

FIG A4 —Lymph node showing typical lymphosarcoma

FIG A5 —The same to show mitoses

FIG A6 —Anaplastic tumour of tonsil secondary in cervical lymph node. Reported as "probably epithelial"

FIG A7 —The same to show epithelial type of cell

the sarcomas. Such specificity cannot help but suggest an important difference in ætiology and development, but at present it can only be said that the question of the exact nature of all the reticuloses remains open.

Brill-Symmer's Disease, also called lympho or giant follicular reticulosis, has a characteristic histological appearance. The huge follicles are packed with lymphocytes with a topography quite different from that of lymphosarcoma. Clinical characters are variable, age incidence is high, there is a slight preponderance of females in our small series, and duration is even longer than in Hodgkin's disease. It is also a reticulosis, the first sign being enlargement of lymph nodes where it usually grows slowly causing little or no disturbance and is sometimes reported as a benign condition. At a later stage, and this may supervene without obvious early signs, it causes generalised and sometimes enormous enlargement of lymphoid tissue throughout the body with extensive œdema and serous effusions. It kills by pressure from the masses of tumour, anæmia and cachexia or by sarcomatous transformation. The average course is longer than that of Hodgkin's disease.

Lymphosarcoma may be regarded as a true sarcoma arising in primitive mesenchyme and differentiating to the production of lymphocytes. The second tumour in this group, the reticulum cell

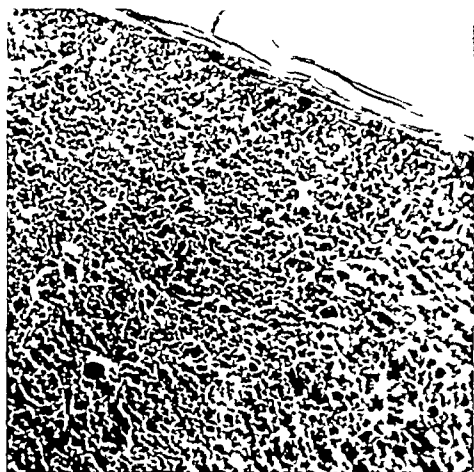


FIG A1

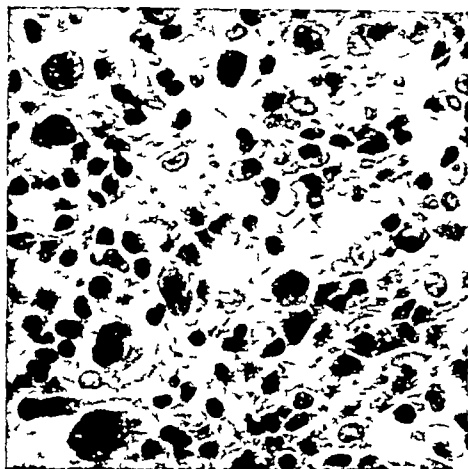


FIG A2



FIG A3

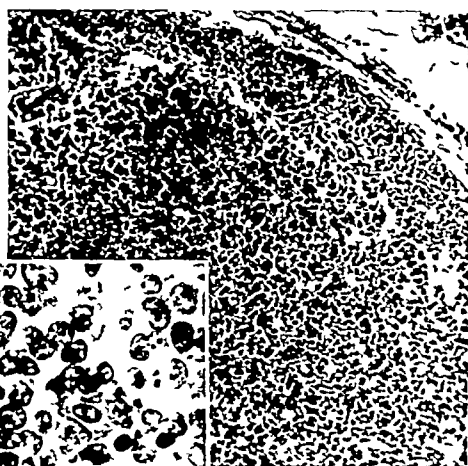


FIG A4

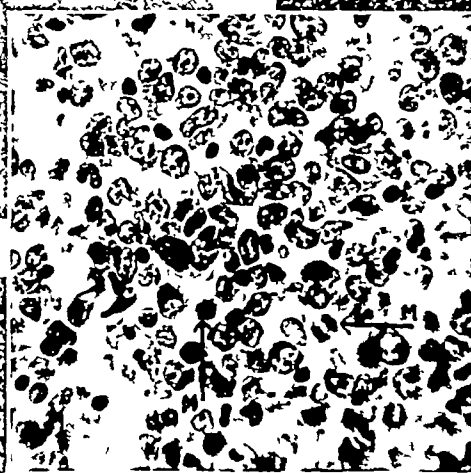


FIG A5

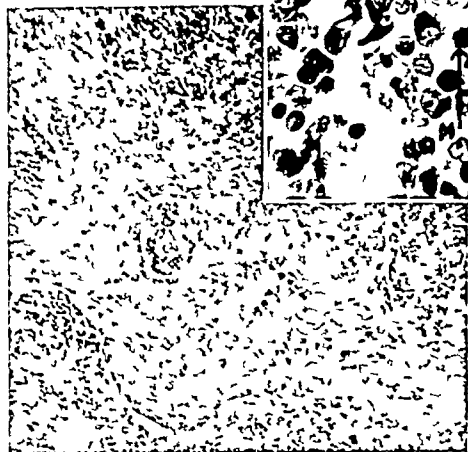


FIG A6

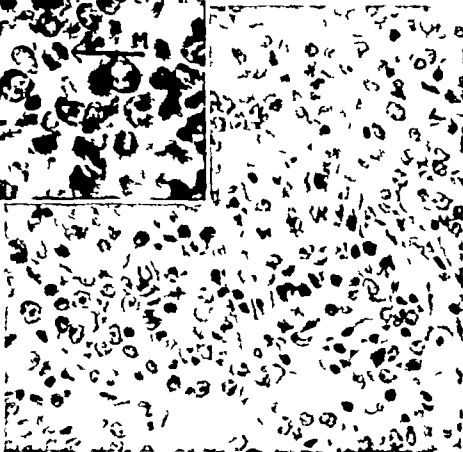


FIG A7

sarcoma, merely shows differentiation towards another type, the reticulocyte. The clinical characters of the two sarcomas are similar. The age incidence is higher and males are less predominant than in Hodgkin's. Duration is comparatively short. Both tumours behave as infiltrating sarcomas, but there may be an apparently multifocal origin in lymph nodes, suggesting kinship with the reticulosis. Lympho-sarcoma is the only neoplasm in the series showing a tendency to develop leukæmia, and sections of lymph nodes from the two conditions are much alike.

Anaplastic Tumours—Under this heading are collected all the tumours with pathological reports expressing doubt as to whether they were sarcoma or carcinoma, including the description "lympho-epithelioma". Here are some typical reports—

"An anaplastic tumour, I do not know whether it is sarcoma or carcinoma, but I think it is reticulum cell sarcoma."

"I think this is an epithelial tumour, but I cannot be sure."

"Malignant cells infiltrating lymphoid tissue, carcinoma, I think."

Clinically the characters of these tumours are almost indistinguishable from those of the more differentiated sarcomas with which they are grouped, except that they are almost entirely confined to the lymphoid tissues of the head and neck. Metastases from them may be found in any organ or tissue. Such a report from axillary or supraclavicular nodes suggests the presence of a primary anaplastic tumour in the lung.

The Leukæmias must also be accepted as reticuloses, and polycythæmia is only omitted because the number of our cases is too small for useful analysis. The blood picture and clinical features are so well known that no description is needed. Diagnostic difficulties may be encountered when multiple enlargement of lymph nodes is combined with a moderately raised white count, but the high proportion of lymphocytes in the circulating blood usually answers doubts and confirms the presence of leukæmia. The atypical signs of aleukæmic leukæmia may be more confusing. The peripheral blood picture may appear normal although other signs of a reticulosis are present, and it is only when the rapid progress of the disease, in spite of apparently appropriate treatment, raises alarm that a marrow smear provides the diagnosis.

ANALYSIS OF MATERIAL

A point has now been reached when, leaving the blood diseases aside, attention can be focused on the two main groups, one containing the two reticuloses, Hodgkin's and Brill-Symmer's diseases, the other the lymphoreticular sarcomas and the anaplastic tumours which may be either sarcomas or tumours derived from primitive epithelial tissue. The knowledge that there are rare variants and transitional forms allows the inclusion of all forms of neoplasia showing similarity of appearance and behaviour, even if this sometimes leads to mistakes in classification. It seems, for instance, that there will be a few reticu-

loses lacking histological character overlapping into the group of sarcomas, and on the other hand some squamous cell carcinomas anaplastic at the point from which a biopsy was taken. The tables which follow have been prepared to show certain similarities and con-

TABLE I

Distribution by Age, Sex and Duration of Symptoms—Hodgkin's and Brill-Symmer's Disease 1940-1957

Pathological Report	Number Treated	Age Groups				Per cent Males	Duration of Symptoms (months)			
		Under 21	21-40	41-60	Over 60		Under 3	3-6	6-12	Over 12
Hodgkin's disease	275	Per cent 20	Per cent 45	Per cent 30	Per cent 5	Per cent 69	Per cent 15	Per cent 19	Per cent 23	Per cent 43
Brill Symmer's disease	24	0	29	54	17	46	0	8	46	46

trasts in support of my thesis that this grouping is reasonable and helpful. The first table compares Hodgkin's and Brill-Symmer's with the age incidence, sex and duration of the disease before the patient

TABLE II

Principal Sites known to have been Involved by Disease—Hodgkin's and Brill-Symmer's Disease 1940-47

Pathological Report	Number Treated	Superficial Nodes Neck Axilla and Groin	Mediastinum and Lung	Nodes Abdomen	Spleen
Hodgkin's Disease	275	Per cent 100	Per cent 50	Per cent 42	Per cent 20
Brill Symmer's Disease	24	100	17	62	37

came for treatment. This is a table of contrasts and is an argument in favour of the two being distinct and individual conditions. This table shows the proportion of patients with disease present in certain

TABLE III

Complications—Hodgkin's and Brill-Symmer's Disease 1940-47

Pathological Report	Number Treated	Early Fever	Early Anaemia	Itching	Serous Effusion
Hodgkin's Disease	275	Per cent 32	Per cent 35	Per cent 10	Per cent 8
Brill Symmer's Disease	24	0	25	0	33

sites whether it was present when the patient was first seen or appeared later. There is a real similarity between the two conditions, both being diseases of the lymph nodes. In Hodgkin's the first site affected was usually the cervical nodes, and spread to mediastinal and hilar nodes was common. Brill-Symmer's disease often presented in the groin,

spreading to iliac and retroperitoneal nodes This accounts for the slight difference in incidence for these sites The complications of fever and anæmia are described as "early" to indicate that they were present when the patient was first admitted to hospital In the terminal stages of disease they become almost universal Comparison of these complications suggests the presence of two members of one

TABLE IV

Distribution by Age, Sex and Duration of Symptoms—Lymphoreticular Sarcomas and Anaplastic Tumours 1940-47

Pathological Report	Number Treated	Age Groups				Per cent Males	Duration of Symptoms (months)			
		Under 21	21-40	41-60	Over 60		Under 3	3-6	6-12	Over 12
Lymphoreticular sarcomas	165	Per cent. 12	Per cent. 22	Per cent. 41	Per cent. 25	Per cent. 57	Per cent. 28	Per cent. 24	Per cent. 22	Per cent. 26
Anaplastic tumours										
More like carcinoma	56	2	30	45	23	54	29	29	29	14
More like sarcoma	100	10	13	38	39	66	37	33	24	6
Total anaplastic tumours	156	7	19	40	33	62	34	31	26	9

family developing in different directions With Table IV a new comparison begins, that of the partly differentiated lymphoreticular sarcomas and the anaplastic tumours The two sarcomas being exactly

TABLE V

Principal Sites known to have been Involved by Disease—Lymphosarcoma, Reticulum Cell Sarcoma and Anaplastic Tumours 1940-47

Pathological Report	Number Treated	Pharynx and Naso-pharynx	Nodes Neck	Nodes Axilla and Groin	Nodes Mediastinum and Abdomen	Metastases Liver Lung Bone.
Lymphosarcoma	108	Per cent. 24	Per cent. 70	Per cent. 82	Per cent. 50	Per cent. 18
Reticulum Cell Sarcoma	57	26	70	44	45	45
Anaplastic Tumours either Sarcoma or Carcinoma	156	63	86	18	25	52

the same are shown together and in contrast with the anaplastic tumours but, even so, there are no important differences in age or sex It is only under duration that a significant difference appears, the shorter interval before anaplastic tumours attracts attention This table separates the differentiated sarcomas and shows slight but significant differences between lymphosarcoma and anaplastic tumours with reticulum cell sarcoma, sometimes like lymphosarcoma and sometimes bridging the gap between them Lymphosarcoma has some characters

like those of the first group and some cases with this diagnosis behave like reticuloses. The possibility that some of these cases were lymphatic leukæmias of slow onset has been mentioned, and it may be worth remembering that during the first half of the period under review Brill-Symmer's disease was not so well known. Included in the group of cases of the reticuloses are one or two first referred to us as lympho-sarcoma, and it is likely that there were some others never correctly

TABLE VI

Principal Sites known to have been Involved by Disease—Sub-Analysis of Anaplastic Tumours 1940-47

Pathological Report	Number Treated	Pharynx and Naso-pharynx	Nodes Neck	Nodes Axilla and Groin	Nodes Mediastinum and Abdomen	Metastases Liver Lung, Bone
More like sarcoma	100	Per cent 59	Per cent 87	Per cent 23	Per cent 33	Per cent 38
More like carcinoma	56	70	96	9	19	49

diagnosed. Even if the total number of incorrect diagnoses was small they could make a perceptible difference in the percentages. This table again shows a sub-analysis of the group of anaplastic tumours. There is only one difference worth noting—the low incidence of involve-

TABLE VII

Distribution by Age, Sex and Duration of Symptoms—Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours 1940-47

Pathological Report	Number Treated	Age Groups				Per cent Males	Duration of Symptoms (months)			
		Under 21	21-40	41-60	Over 60		Under 3	3-6	6-12	Over 12
Hodgkin's disease	275	Per cent 20	Per cent 45	Per cent 30	Per cent 5	Per cent 69	Per cent 15	Per cent 19	Per cent 23	Per cent 43
Lymphoreticular sarcomas and anaplastic tumours	321	10	20	41	29	59	31	27	24	18

ment of nodes other than cervical nodes in tumours which may be carcinomas. None of the differences are statistically significant and no reason is found for separating this group into two sections.

I believe that the three preceding tables show enough similarity to allow the lymphoreticular and anaplastic tumours to be regarded as a single group for comparison with Hodgkin's disease. Brill-Symmer's is omitted because of the small number of cases. In Table VII the figures are of an order to make all the differences shown significant. There is thus no doubt as to the importance of the differences except that there is an overall preponderance of males. Table VIII shows signi-

ficant differences for incidence in every site except for metastases in lung, liver and bone. Such metastases are nearly always a terminal sign. In the sarcomas they appeared as a rule within two years of treatment, or in generalised cases were present when the patient sought treatment and were the cause of early death. In Hodgkin's disease they usually appear in the later stages of a long illness, so that the apparent similarity is less obvious clinically. This table should be

TABLE VIII

Principal Sites known to have been Involved by Disease—Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours 1940-47

Pathological Report	Number Treated	Pharynx Nasopharynx	Nodes Neck	Nodes Mediastinum and Abdomen	Other Nodes	Spleen	Metastatum Liver Lung Bone
Hodgkin's disease	275	Per cent. 0.4	Per cent. 90	Per cent. 82	Per cent. 58	Per cent. 20	Per cent. 37
Lymphoreticular sarcomas and anaplastic tumours	321	45	75	35	43	6	35

compared with Table V which shows the sites of involvement in the second group. A comparison of the incidence of complications again shows important differences between the two groups.

TABLE IX

Complications—Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours 1940-47

Pathological Report.	Number Treated	Fever	Itching	Serous Effusion	Anæmia.
Hodgkin's Disease	275	Per cent. 32	Per cent. 10	Per cent. 8	Per cent. 35
Lymphoreticular sarcomas and ana- plastic tumours	321	0	0	2	9

DISCUSSION OF TABLES

I have now taken two conditions, Hodgkin's disease and Brill-Symmer's disease, so distinct in character that they can be easily recognised, but showing a family resemblance strong enough to prove a relationship, and have compared them with three tumours of varying histological type, brought together as another family whose ancestry is the same but whose development is different. The members of the first family are reticulososes affecting lymph nodes and only involving other tissues and organs at a late stage of the disease. Their systemic manifestations play an important part in prognosis. The second family consists of malignant tumours arising in, or in association with,

lymphoreticular tissue infiltrating locally and producing secondary deposits in lymph nodes and distant metastases. Between the two families are some of the transition forms mentioned by Willis, and in the second family are found some atypical members which may be intruders from another family altogether, the carcinomas. This does not alter the fact that it is now possible to separate this apparently heterogeneous collection of neoplasms into two main groups. One of these consists of lymphoreticular disease multifocal in origin in the sense that all lymphoreticular tissue in the body either simultaneously, or in an order which cannot be predicted, responds to an unidentified stimulus by hyperplasia going on to neoplasia. The other consists of a group of malignant tumours mainly lymphoreticular sarcomas but including some completely anaplastic growths, unifocal in the sense that there is a primary tumour which gives rise in the ordinary way to secondary deposits in lymph nodes and distant metastases. If this essential contrast is accepted it is not surprising that the groups call for different treatment and respond differently to treatment given.

METHODS OF TREATMENT

Before discussing methods of treatment it is important to find some way of assessing the degree of advancement of the cases forming the sample treated. Where malignant disease is concerned the idea of staging is familiar. For the forms of neoplasia now in question there is only one division, but a division of such importance that treatment is almost entirely determined by it. This division is into localised and generalised disease and is applicable to all lymphoreticular neoplasia of both groups. The nature of these diseases with their tendency to multifocal manifestations makes it necessary to define what is meant by a localised lesion. Our definition of a localised lesion is that the neoplasia is, as far as can be ascertained, confined to one region of the body. This is meaningless until the regions are themselves defined, and it must be admitted that our regions are not those of the anatomist. They are best described as parts of the body which can be conveniently treated by X-rays to a dose believed to be capable of producing complete and permanent resolution of sensitive tumours. These regions are—head and neck to the level of the clavicles, the mediastinum, each axilla and each groin. The abdomen can also be regarded as a region if only lymph nodes are involved. The disease is regarded as generalised when two or more of these regions are involved, or when in addition to regional nodes organs such as spleen, liver, lung or bones are the site of tumour formation.

At this point I should like to say that I confine my discussion of treatment to X-ray therapy, which I still regard as by far the most important means of treating all these diseases. In Manchester we divide our techniques into radical and palliative and usually make a deliberate choice of one or the other before beginning treatment. In

general, radical techniques are used for localised, and palliative techniques for generalised lymphoreticular tumours with the variations called for by difference in the sites affected and the age and general condition of the patient

THE TREATMENT OF HODGKIN'S AND BRILL-SYMMER'S DISEASES

It has been agreed that both these diseases are by their nature generalised reticuloses, but it often happens that the first sign is enlargement of one group of lymph nodes, possibly a single lymph node. The patient seldom seeks advice before signs of new growth in the nodes are obvious and may wait till several groups of nodes have grown to a large size, even so, about one-third of the patients come for treatment with the disease still confined to a single region and thus, by our definition, localised. In spite of the probability that as they are true reticuloses new foci will soon appear in other sites there may be a long interval before extension occurs, and radical treatment should be tried. It has been claimed that surgical dissection of the affected nodes may cure the early case. We believe that radiotherapy to sufficient dosage may be equally effective. In certain selected cases, therefore, the radical methods to be described for the treatment of the radio-sensitive sarcomas are appropriate for early Hodgkin's or Brill-Symer's disease.

Unfortunately, it is more usual to be faced with the problem of a generalised reticulosis. There are several groups of enlarged lymph nodes and possibly such signs of failing health as fever with night sweats and a falling red blood count. Treatment must then be palliative. We use two X-ray techniques, a chasing technique and a low dose palliative technique of regional type. The first is preferred when there are several foci of disease and treats each focus separately, using fields which cover the lesion but without a wide margin, and gives a dose high enough to produce at least temporary disappearance while avoiding severe reactions. This technique conserves tolerance by treating only a small volume of tissue but to dosage likely to be biologically efficient within the volume irradiated. The tolerance will be needed for the treatment of the new manifestations which will continue to appear until finally they can no longer be controlled.

TREATMENT OF THE LYMPHORETICULAR SARCOMAS

The tumours in my second group are more often treated while they are still localised, possibly because tumours of the pharynx and nasopharynx, where they tend to be located, inconvenience the patient and he consults his doctor within a comparatively short time. In the treatment of localised lymphoreticular neoplasia, and this applies also to the first group, the guiding principle is that it is necessary to include not only the visible or palpable tumour but also the group of lymph nodes reached by the lymphatics draining the area and any probable line of extension, for instance, the foramina at the base of the skull

if the tumour is in the nasopharynx This means that the fields must be very large A frequent arrangement uses four fields to cover the whole head and neck from a line above the base of the skull to below the clavicles or neck and mediastinum (Fig B10) The axilla and groin are easier to treat, but even there the homolateral supraclavicular nodes or entire iliac fossa must be included When treatments of this order are under consideration it is necessary to balance the volume of tissue to be treated against the dose which can be tolerated The questions of local tolerance of skin, mucous membrane and connective tissue have been much discussed and are fairly well understood, but here we are dealing with something more than local tolerance and in many cases a considerable systemic effect must be expected In the treatment of the head and neck severe reactions are produced in the mouth and throat Taste and smell may be lost and the secretion of the salivary glands is reduced, so that it becomes difficult to maintain nutrition If part of the abdomen is included, any irradiated viscera

TABLE X

Clinical Features of Three Types of Leukæmia 1940-47

Pathological Report	Number Treated	Nodes Neck	Other Nodes	Spleen	Early Anæmia
		Per cent	Per cent	Per cent	Per cent.
Myeloid	64	0	0	100	81
Lymphatic	57	74	95	77	35
All acute and aleukæmic	36	70	78	75	100

will react and both bowel and kidney are radiosensitive organs In addition the radiation of large sensitive tumours must result in the breaking down of their constituent cells with liberation of toxic products which must be excreted The general tolerance of the patient is thus under considerable strain and the dose to be given is determined by the sum of the local and general effects These effects are, however, temporary and are not too heavy a price to pay for the chance of cure

When the lymphoreticular sarcomas are generalised it can be said that multiple metastases are present Cure is almost impossible, but good palliation can be obtained because of the radiosensitivity of these tumours The techniques used are those already described for the treatment of the generalised reticulosis, but they are less effective for the sarcomas because vital organs are invaded Post-mortem examinations on some of our cases showed nearly every organ in the body to contain secondary deposits

THE LEUKÆMIAS

Before the results of treatment are described this survey of the reticuloses is completed by two tables comparing the clinical findings in the leukæmias Again I have simplified the table by making only three groups, chronic myeloid leukæmia, chronic lymphatic leukæmia



Fig B1 —Patient with Hodgkin's disease
in cervical lymph nodes



Fig B2 —Secondary deposits in body
of vertebra in Hodgkin's disease



FIG B3 —Sarcomatous involvement of subcutaneous tissues and muscle in
Brill Symmer's disease

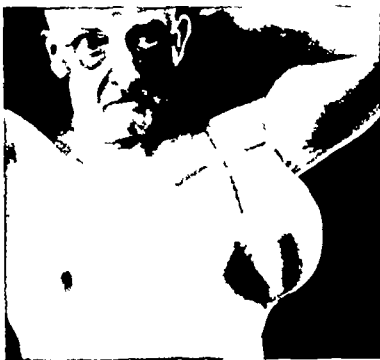


FIG B4 —Lymphoma in axillary
and supraclavicular lymph nodes



FIG B5 —The same one month after
completing regional X ray therapy
Central dose 3000 r

and all acute and aleukæmic types taken together, inaccurate but convenient as their prognosis is uniformly bad. The three types are obviously completely different. Myeloid leukæmia shows the characteristic blood picture and enlargement of the spleen, lymphatic leukæmia effects the production of lymphocytes in nodes as well as marrow, but enlargement of the spleen and anæmia are less common, at least in the earlier stages. Acute leukæmia affects every part of the hæmopoëtic system, and up till now has proved almost completely resistant to all

TABLE XI
Clinical Features of Lymphosarcoma and Lymphatic Leukæmia 1940-47

Pathological Report	Number Treated	Neck Nodes Involved	Other Nodes Involved	Spleen	Anæmia	Leukæmia
Lymphosarcoma	108	Per cent 70	Per cent 82	Per cent 14	Per cent 16	Per cent 100
Lymphatic leukæmia	57	74	95	77	35	8

forms of treatment. This is a comparison between lymphatic leukæmia and lymphosarcoma to bring out the similarity which has already been mentioned. The differences are seen in the percentages of cases with enlargement of the spleen, and with leukæmia present.

TABLE XII
Radiotherapy Results of Localised Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours

Pathological Report.	Number Treated	1940-1945					
		Alive 3 Years		Alive 5 Years		Well 5 Years	
		Number	Crude Rate	Number	Crude Rate	Number	Crude Rate.
Hodgkin's disease	42	29	Per cent 69	23	Per cent. 55	10	Per cent. 24
lymphoreticular sarcomas and anaplastic tumours	115	71	62	59	51	55	48

The leukæmias recorded here were all treated in one of two ways, either by X-ray therapy to the spleen or by chemotherapy using urethane. The second method was only used towards the end of the period and seldom as the only therapy, X-ray having played some part, so when the results are given the two methods cannot be separated.

RESULTS OF TREATMENT

The figures given are all crude survival rates showing the percentage of the patients treated alive at a chosen anniversary, in this case the third and the fifth. Patients reported as "well" had no sign of disease when examined for the record and had needed no further treatment after the first course. This table compares the results obtained in

localised Hodgkin's disease with those of the lymphoreticular sarcomas at three and five years. There is little difference in the survival rates but in the last column the proportion of cases recorded as "well" shows that long survival in Hodgkin's disease is often associated with slow extension and long remission after treatment whereas the sarcomas,

TABLE XIII

Radiotherapy Results of Generalised Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours

Pathological Report	Number Treated	1940 1945					
		Alive 3 Years		Alive 5 Years		Well 5 Years	
		Number	Crude Rate	Number	Crude Rate	Number	Crude Rate
Hodgkin's disease Lymphoreticular sarcomas and anaplastic tumours	109	25	Per cent 23	12	Per cent 11	2	Per cent 2
	77	14	18	5	6	3	4

unless metastases appear, may be permanently controlled. A number of ten year survivals among the earlier cases of sarcoma show that this is possible.

Although histology is the determining factor there are others which also influence prognosis. Tumours confined to the head and neck have

TABLE XIV

Radiotherapy Results—All Cases Hodgkin's Disease, Lymphoreticular Sarcomas and Anaplastic Tumours

Pathological Report	Number Treated	1940 1947		Number Treated	1940 1945	
		Alive 3 Years			Alive 5 Years	
		Number	Crude Rate		Number	Crude Rate
Hodgkin's disease Lymphoreticular sarcomas and anaplastic tumours	275	85	Per cent 31	151	32	Per cent 21
	321	128	40	192	69	36

a good prognosis, in spite of the fact that some of them may be more resistant carcinomas, and should be given full treatment even if a large tumour is accompanied by bilateral enlargement of lymph nodes. Prognosis is also good when the disease is confined to a single group of superficial lymph nodes, but such limitation is rare.

I have no survival figures at five years for Brill-Symmer's disease because only 3 cases with this diagnosis were treated more than three years ago. At the third anniversary 8 of the 24 cases, none of which

was localised, were alive Only one was well The generalised cases of Hodgkin's disease and of lymphoreticular sarcoma show an equally bad prognosis

The results for all cases, localised and generalised combined, are given in this table in which are shown the three year results of all cases treated up to 1947 assessed at the third anniversary They still show a significant advantage for the sensitive sarcomas, using this term to

Comparison of survival rates in Hodgkin's disease and lymphoreticular sarcoma.

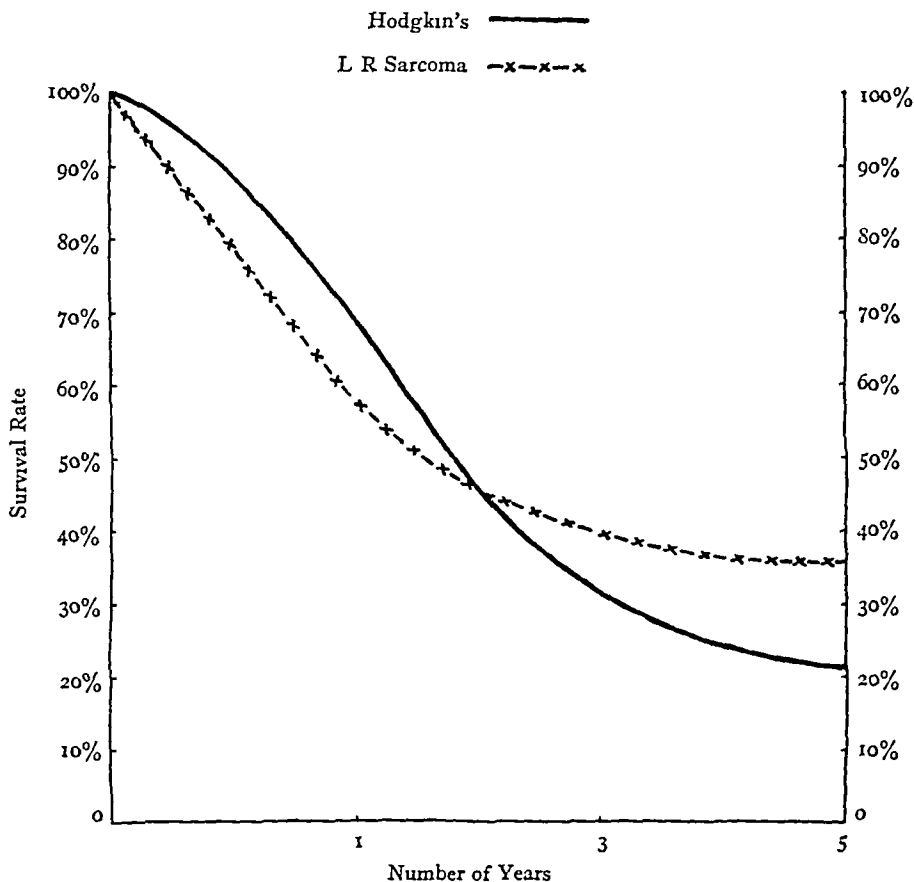


FIG C —Five year survival curve for Hodgkin's disease and lymphoreticular sarcoma

include all the malignant tumours of the second group The generalised sarcomas are a smaller proportion of the whole but they are so rapidly fatal that they depress the survival curve of the sarcomas This curve is contrasted with that of Hodgkin's disease on a graph To complete this presentation of results the next table shows those obtained in the treatment of the three forms of leukaemia There is little difference between the prognosis of the chronic forms That of the acute forms is so bad that not one of these cases survived for one year The last table compares the results in Hodgkin's disease and the leukaemias

Those in leukæmia are the worse of the two, and this is even more obvious at five years when the survival of leukæmia falls to 3 per cent

FINAL DISCUSSION

It may seem to you that I am merely restating the obvious when I draw your attention to the great difference in prognosis which appears as soon as these diseases become generalised. The prognosis for localised sarcoma, even of a most malignant type, is as good as that of squamous cell cancer in the mouth with no involvement of lymph

TABLE XV

Treatment Results of Leukæmias

Pathological Report	Number Treated	1940 1947	
		Alive 3 Years	
		Number	Crude Rate
Myeloid	64	19	Per cent 30
Lymphatic	57	14	25
Acute and aleukæmic	36	0	0

TABLE XVI

Treatment Results—Hodgkin's Disease and Leukæmia

Pathological Report	Number Treated	1940 1945	
		Alive 3 Years	
		Number	Crude Rate
Hodgkin's disease	275	85	Per cent 31
Leukæmias	157	33	21

nodes, yet the staging of sensitive sarcomas includes bilateral involvement of the cervical nodes in the localised group. The prognosis of the true reticulososes, even when localised, is less good, and that of all generalised lymphoreticular neoplasia is frankly bad. It is true that all malignant disease is much less likely to be cured once it has spread beyond the primary site, so why should anything different be expected of the lymphoreticular tumours? There is, however, a difference. These tumours are radio-sensitive and do not need very high doses to ensure complete disappearance, so that many attempts have been made to achieve this by treating all sites of neoplasia, including irradiation of the whole trunk. Unfortunately, success has not been obtained

because even with the most radio-sensitive of the tumours the general tolerance of the patient is scarcely ever good enough to allow the necessary dosage to be delivered to all foci of disease either by treating all at once or by treating them in rapid succession

The question of the combination of local and general tolerance which allows the successful treatment of one of our regions has already been discussed. The tolerance needed for the treatment of generalised disease is that of the individual as a whole. There are two main reactions of systemic intolerance, one immediate, radiation sickness, and one delayed, changes in the blood picture due to destruction of stem cells in the marrow and of sensitive cells in the circulating blood. The first of these reactions can to a great extent be avoided by careful gradation of dosage, beginning with a small daily dose and increasing to the desired level with careful attention to effect and is not, in my experience, a frequent cause of failure. The limiting factor which makes it impossible to give curative doses of very large volumes is the inclusion of too much of the blood-forming marrow. Effect on marrow is reflected by changes in the circulating blood. All elements are diminished, white cells, platelets, and to a lesser degree red cells, and the degree of change is related to the normal life of the cell in the blood stream and the speed of replacement. The first cells to show a decrease in the number circulating are the lymphocytes, then the leucocytes, the platelets and, finally, the erythrocytes. It is probable that when large volumes, for instance 25 per cent of the tissues of the body, are irradiated these decreases are proportional to the doses given provided that other factors are constant. I am not concerned here with the results of whole body radiation to single high doses such as may occur with atomic bombing but with the effect on hæmopoiesis of doses of the order needed to secure resolution of sensitive tumours. Experience has shown that at least half the trunk can be irradiated to the necessary dose level if suitable fractionation is used. The total white count of peripheral blood will fall to a low level with the lymphocytes leading and indicating the speed of total drop. We regard a count of 2000 total white cells as an indicator of risk, but when the clinical condition was good we have taken our white counts as low as 1000 total whites with no permanent ill effects. After the appearance of the leucopenia, the platelet count also falls, and there is little doubt that there is not only damage to the megakaryocytes but also to the whole erythropoietic series in the marrow. If the proportion of blood-forming marrow which is irradiated is not too big, hypertrophy outside the irradiated volume maintains the necessary replacement, and in time recovery takes place. The failure of erythropoiesis is, therefore, masked because the long life of the red cell in the circulation gives time for hypertrophy and recovery. When the damage has been spread over more of the marrow enough may not be spared to allow hypertrophy to meet the need for replacement, and partial recovery will not be enough to prevent the appearance of anæmia. Severe injury may result in complete aplasia

of all elements in the treated marrow with death from aplastic anæmia unless the patient dies at an earlier stage from infection. It is, of course, not only in the terminal stages that infection is a danger but throughout the period while the counts are low. A low leucocyte count interferes with the normal mechanism of defence but does not altogether prevent the usual response. Lymphocytopenia may be almost more important because the lack of lymphocytes results in loss of the antibodies normally produced by them. All these effects can be obtained by the irradiation of the normal individual. When the marrow is already the site of disease, as in the reticuloses, and the patient is suffering from fever, septic ulceration or malnutrition, the dangers are much greater. It seems, then, that the attempt to irradiate all foci of generalised disease must be renounced. We tried to overcome the difficulties by irradiating the whole trunk in strips each of which in turn received a dose which we hoped might prove to be biologically effective but we were not successful, and I do not believe that the various forms of whole body radiation described as telorœntgen therapy can claim any strikingly good results. Must we then admit that there is no hope for the many patients suffering from generalised lymphoreticular neoplasia? I fear we must, if complete and permanent cure is in question. The development of chemotherapy for these diseases is, therefore, very welcome, and further research is much needed. The most important response so far has been that of Hodgkin's disease to the nitrogen mustards. In some cases almost complete remission is obtained and lasts for many months, in others, remissions are much shorter though transient improvement is nearly always found.

In my opinion, useful though chemotherapy is, it should not be the first treatment used, because I believe that in the early stages while systemic symptoms are not severe, local lesions can be controlled by the chassing technique with practically no effect on hæmopoiesis even when several masses of lymph nodes have to be irradiated. The undesirability of any treatment which seriously interferes with erythropoiesis has already been stressed and is as important for chemotherapy as it is for radiotherapy. On the other hand there are many cases when the problem is one of acute discomfort from fever, sweating and itching, and nitrogen mustard then gives genuine relief.

The drug, triethylenemelamine, belongs to the same group and can be taken by mouth. The immediate effects are less disagreeable and it is proving useful not only for Hodgkin's disease but for the leukæmias. Urethane also can be used for leukæmia and we prefer it to nitrogen mustard for this purpose. Various other drugs are now on trial, and may improve on any results so far obtained. At present, however, a drug has yet to be found without a damaging effect on the marrow cells which must limit its use.

Before finishing, the use of radioactive isotopes must be mentioned, but so far their role in the treatment of the lymphoreticular neoplasms has been unsatisfactory. Radioactive phosphorus has a place, though

no more important than that of X-rays in the treatment of leukæmia, but it has been tried with little success for the other reticuloses, and now few advocate further trial. The possibility of finding a substance into which a suitable radioactive isotope could be inserted for differential absorption, analogous to that of iodine in the thyroid, maintains the hope that some day radio-sensitive tumours may be destroyed by radioactivity from within.

CONCLUSIONS

1 All localised tumours with pathological reports suggesting that they may be lymphoreticular sarcoma should be treated by regional X-ray therapy to full dosage. This can save at least 40 per cent of localised cases.

2 The treatment of generalised lymphoreticular tumours, true reticuloses and sarcoma should be in the first place by palliative X-ray therapy which should aim at conserving the general tolerance of the patient.

3 Chemotherapy may be a useful adjunct but should be restricted to the later stages.

4 A biopsy is essential when lymphoreticular neoplasia is suspected.

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IRON ABSORPTION TESTS IN ANÆMIA THE USE OF INTRAVENOUS IRON PREPARATIONS

By JOAN CRAWLEY, M B, Ch B, M R C P Ed

From the Department of Medicine, University of Edinburgh

IN recent years, following the work of Nissim (1947), who described a method of preparation of saccharated oxide of iron, there has been a revival of interest in the administration of iron preparations by the intravenous route

The use of saccharated oxide of iron has been described by Davidson and Girdwood (1948), Slack and Wilkinson (1949), Govan and Scott (1949), Sinclair and Duthie (1949, 1950) and others

The purpose of the present paper is to give an account of the response to intravenous iron in patients with iron deficiency anæmia who had failed to improve with prolonged courses of iron by mouth

In addition, since there was a possibility that the failure in response to oral therapy was due to malabsorption of iron, a test for iron absorption has been applied to many of these patients, to a series of control cases and to patients suffering from other forms of anæmia

Finally, in view of the importance of knowing to what extent iron administered intravenously is excreted, certain experiments have been carried out to measure the excretory capacity of the body for the metal

ABSORPTION OF IRON METHODS AND RESULTS

In all instances where the condition has been described as refractory, the patient had a prolonged period of treatment with oral iron preparations, including at least three weeks of this form of therapy in hospital

When it was sufficiently established that there was no response to iron by mouth, the patients were given intravenous injections of the preparation of saccharated oxide of iron marketed as "Ferrivenin" in divided doses to a total of from 1 to 1.8 gm.

Iron absorption curves were carried out on the lines suggested by Moore and Doan (1936) and Moore *et al* (1939). These workers showed that, following the ingestion of iron, there is a prompt rise in the serum iron level, apparent in the first half hour, reaching a maximum in two and a half to five hours, and gradually falling to approximately the basal level in twelve hours. They concluded that although the test did not measure the total amount of iron absorbed, it did indicate the presence of absorption and gave some idea of its degree. It was therefore felt that a test of this nature might be of value in demonstrating the presence or absence of iron absorption in these cases of hypochromic anæmia refractory to oral iron.

On the day of the test, the patients' breakfast was restricted to a cup of tea and a piece of bread, since the taking of food is reputed to lower the serum iron content (Moore *et al*, 1939).

Blood samples were withdrawn before the ingestion of the test dose of iron and at two, four, six and sometimes twenty-four hours thereafter

In the early stages of the investigation, the patients were given 9 grains of ferrous sulphate (approximately 2 mgm per kilogram of body weight) as a test dose. It was found, however, that the average rise of serum iron with this dosage was only $36 \mu\text{g}/100 \text{ ml}$ of serum. Since it had been demonstrated by Moore *et al* (1939) that over a twenty-four hour period the serum iron of patients on a mixed diet may show an hourly fluctuation of $35 \mu\text{g}/100 \text{ ml}$, it was decided to increase the test dose to 18 grains of ferrous sulphate.

Unfortunately, however, certain cases had to be eliminated from the study because of nausea, vomiting or diarrhoea resulting from the administration of this larger dosage.

Serum iron estimations were carried out by a modification of the method of Dahl (1948) in which the iron is oxidised by nitric acid and the colour is developed by potassium thiocyanate. The danger of co-precipitation of some of the serum iron along with the proteins is obviated in this procedure by the denaturation of the proteins by heat before their precipitation with trichloroacetic acid.

Urinary and faecal iron was measured as follows. An aliquot of the specimen was dry ashed, the ash being dissolved in iron-free hydrochloric acid and four drops of nitric acid added to the hot solution. After cooling, 2 c.c. of 20 per cent potassium thiocyanate was added, the solution centrifuged and the colour compared with the standard in a Spekker photoelectric absorptiometer*.

Response to Intravenous Iron of Patients Refractory to Iron Preparations given by Mouth—In Table I there are given the results of intravenous iron therapy in 13 patients with hypochromic anæmia who showed no response to the prolonged administration of iron by mouth. It will be seen that in all these patients there was a satisfactory rise in hæmoglobin.

The following information about these patients is of interest.

Cases 1, 2 and 3 were examples of the sprue syndrome, a condition in which the clinical features are the direct result of malabsorption and the anæmia is frequently refractory to the usual forms of treatment. Six months after Case 1 had been treated with 1.8 gm of ferrivenin, the patient developed a macrocytic anæmia with a megaloblastic marrow, which failed to respond to liver injections (vitamin B₁₂ not then being available) but responded readily to folic acid. When the patient was seen six months later, there was no return of the iron deficiency anæmia despite the fact that no further iron therapy had been given.

In Case 5, although fat-balance tests revealed no evidence to support a diagnosis of the sprue syndrome, the hæmatological features

* This work was done in 1948 and 1949. More recently other workers have obtained significantly higher results in estimating serum iron levels, but this in no way detracts from the validity of the comparisons or conclusions—L. S. P. Davidson.

TABLE I
Response to Intravenous Iron of Patients Refractory to Iron Preparations given by Mouth in Hospital

Name	Age	Sex	Cause of Anæmia	Blood Findings before Injections			Gm of Iron given I V	Blood after Injections		
				Hb (per cent)	R B C (M/c mm)	C I		Hb (per cent)	R B C (M/c mm)	C I
1 M F	35	F	Steatorrhœa	56	3 49	0 80	1 8	100	4 80	1 04
2 B L	13	F	Cœliac disease	62	4 50	0 69	0 5	90	4 48	1 00
3 W S	22	M	Cœliac disease	56	4 69	0 60	1 2	102	5 01	1 02
4 M G	41	F	Idiopathic	56	4 01	0 70	1 2	90	4 80	0 94
5 M C	61	F	Idiopathic	62	4 32	0 72	1 0	100	5 00	1 00
6 I M	58	F	Gastro enterostomy	62	3 74	0 83	1 2	108	5 00	1 08
7 A G	39	F	Partial gastrectomy	48	4 32	0 56	1 0	100	4 84	1 03
8 A M	74	F	Idiopathic	64	3 74	0 86	0 7	94	4 46	1 05
9 H M	38	F	Idiopathic	64	4 00	0 80	1 1	96	5 24	0 92
10 R H	37	F	Idiopathic	68	5 41	0 63	1 0	102	4 50	1 13
11 J M	40	F	Idiopathic	50	3 56	0 70	1 1	100	4 90	1 02
12 W B	26	F	Idiopathic	66	4 82	0 68	1 2	90	5 00	0 90
13 A M	35	F	Pregnancy	54	4 12	0 66	1 5	86	4 46	0 96

were somewhat similar. The patient had a refractory idiopathic iron-deficiency anæmia with a normoblastic marrow and received intensive oral iron therapy for a year with no response. The marrow then became megaloblastic and a hypochromic macrocytic blood picture developed in the peripheral blood. There was no response to the refined liver preparation "Anahæmin" but a rapid response ensued when folic acid was given, the marrow reverting to the normoblastic state with an associated rise in red cells. Despite this, the refractory iron deficiency persisted until treatment with "Ferrivenin" was given.

These two cases support the view of Davidson and Girdwood (1947) that certain cases of "idiopathic" refractory megaloblastic anæmia are probably due to malabsorption despite the absence of diarrhœa or steatorrhœa.

TABLE II

Iron Absorption Tests in Normal Individuals
Serum Iron (μg per 100 ml Serum)
 (Test dose = 18 grains of ferrous sulphate)

Name	Fasting Level	2 Hour Level	4 Hour Level	6 Hour Level	Rise in Serum Iron.
J D	53	200	160	103	147
I G	64	166	200	116	136
M B	40	58	175	133	135
N H	58	183	146	140	125
M W	40	230	250	80	210
C H	106	220	193	160	114
Average maximal rise in serum iron = 145					

Case 6 had a gastroenterostomy and Case 7 a subtotal gastrectomy it is reasonable to assume that malabsorption played some part in the failure of these patients to respond to oral iron therapy. In the remaining cases in Table I no satisfactory explanation of their refractoriness to oral therapy was discovered. Accordingly it was decided to make an investigation of the absorption of iron in normal individuals and in patients suffering from anæmia of various types.

Iron Absorption Curves in Normal Individuals—Curves were carried out on six apyrexial patients in whom the blood picture and blood count were normal. The test dose of 18 grains of ferrous sulphate was given by mouth. The results are given in Table II.

The average rise in serum iron in these cases was $145 \mu\text{g}$ per 100 ml the maximal being $210 \mu\text{g}$ per 100 ml, the minimal $114 \mu\text{g}$ per 100 ml. Accordingly a rise in serum iron of $100 \mu\text{g}$ per 100 ml is here taken to be the arbitrary lower limit of normal in persons receiving a dose of approximately 4 mg of iron per kilogram of body weight. Any curve showing a smaller rise than $100 \mu\text{g}$ per 100 ml is considered to be abnormally flat. If this be true for normal persons

it is even more significant for anæmic patients since Balfour, Hahn *et al* (1942) have shown that there is increased absorption of iron in anæmic individuals

Iron Absorption Curves in 19 Cases of Iron-Deficiency Anæmia—The results are as shown in Table III. An average rise in serum iron of $236 \mu\text{g}$ per 100 ml was obtained, a figure which suggested that satisfactory absorption of iron had occurred. This suggestion received confirmation when it was shown that subsequently all these patients responded satisfactorily to iron preparations given by mouth.

Iron Absorption Curves in Allegedly Refractory Iron-Deficiency Anæmia—It has been the experience of the staff at the Hæmatological Clinic at Edinburgh Royal Infirmary that many patients with so-called "refractory" iron-deficiency cease to be refractory when iron therapy is given in hospital. This is usually due to the patient on treatment at home taking the iron preparation irregularly.

Twenty of the patients referred on account of such a "refractory" state had iron absorption tests carried out. The results are given in Tables IVA and IVB.

A study of Table IVA shows that cases 1-15 absorbed iron satisfactorily as judged by the rise in serum iron, and responded satisfactorily to subsequent oral iron therapy.

It will be seen from Table IVB, on the other hand, that five flat curves were obtained in Cases 16-20.

In none of these cases was there any response to continued oral iron therapy given under supervision, although the patients all responded dramatically to subsequent parenteral iron. Unfortunately this form of therapy had to be abandoned in Case 16 because of severe reactions. This is the only case in this series in which unpleasant reactions to "Ferrivenin" were encountered. The information given in Tables II, III and IV is summarised in Graph 1.

Iron Absorption Curves in Macrocytic Anæmia—Absorption tests carried out on 10 patients are shown in Table V. Cases 1-7 had Addisonian pernicious anæmia and 8-10 had macrocytosis with normoblastic or macro-normoblastic marrow.

The average fasting serum iron for the ten curves was $138 \mu\text{g}$ / 100 ml with a rise of only $27 \mu\text{g}$ / 100 ml and that for the 7 cases of pernicious anæmia was $174 \mu\text{g}$ / 100 ml with a rise of $18 \mu\text{g}$ / 100 ml.

In cases 9 and 10 there was iron deficiency in addition to macrocytosis. Case 9 had a markedly shortened small intestine due to previous gut resection. The anæmia responded to parenteral iron given with protein, vitamins and folic acid by mouth.

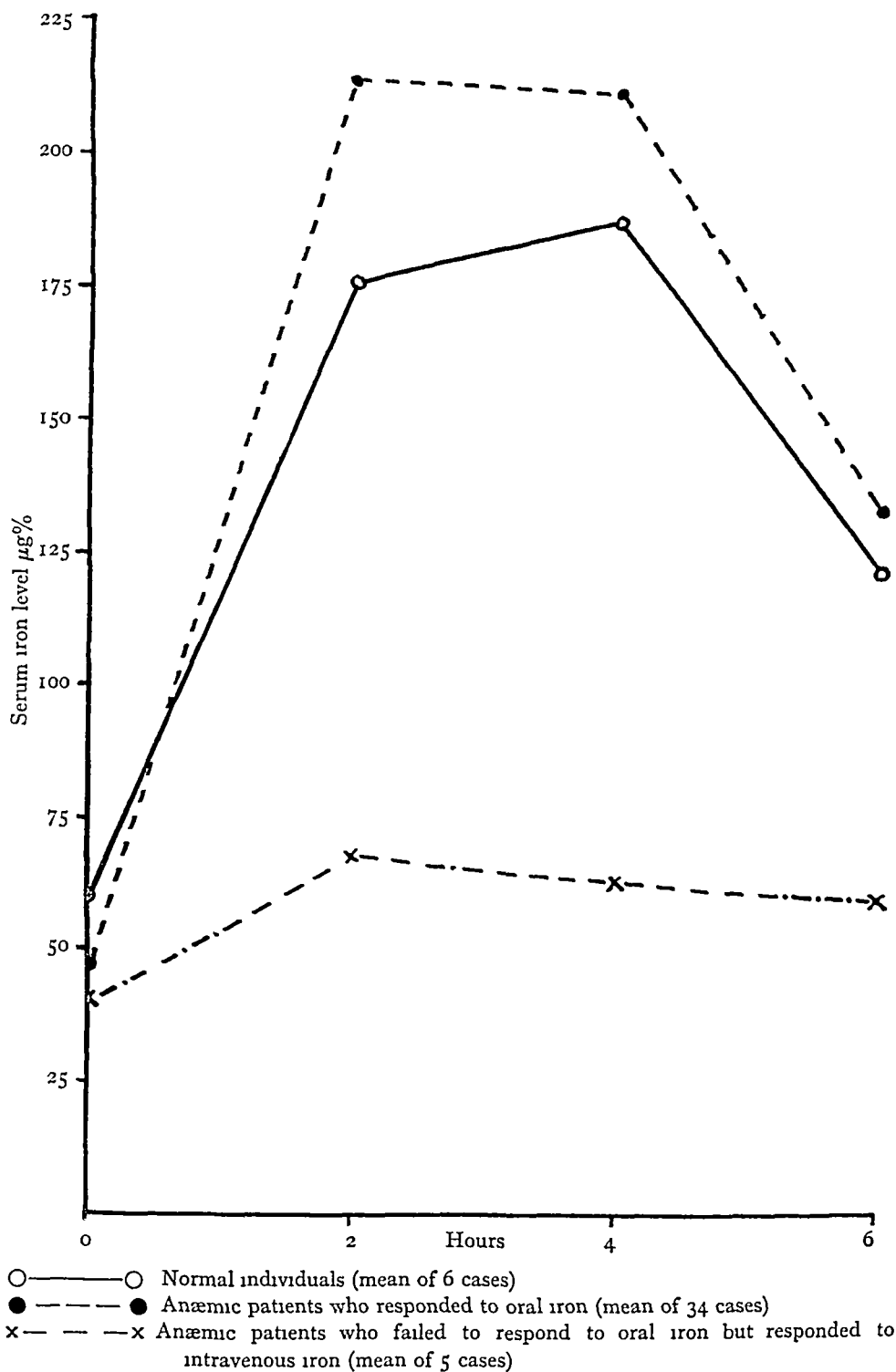
The serum iron level in pernicious anæmia invariably falls within the first few days after specific treatment (Cartwright *et al*, 1948). This is supposedly due to the rapid utilisation of the iron by the newly formed red cells and usually follows the reticulocyte rise. The fall is more precipitate in those cases receiving vitamin B₁₂, liver or folic acid by injection than by mouth.

IRON ABSORPTION TESTS IN ANEMIA

TABLE IVB
Iron Absorption Curves in Patients Allegedly Refractory to Iron by Mouth
(Test dose = 18 grains ferrous sulphate)

Iron Curves in Patients Allegedly Refractory to Iron by Mouth (Test dose = 18 grams ferrous sulphate)										IRON TESTS IN AN										
Case	Blood before Treatment				Serum Iron Levels in μg per cent				Blood after Treatment with Iron by Mouth in Hospital				Blood after Intravenous Iron						Gm I.V. Iron given	
	Hb per cent	RBC M/cmm	CI	P CV per cent	Fasting	2 hrs	4 hrs	6 hrs	Rise	Hb per cent	RBC M/cmm	CI	P CV	Hb per cent	RBC M/cmm	CI	P CV	Serum Iron μg per cent		
16	48	3.52	0.68	27.5	46	67	63	67	21	50	3.42	0.73	28.5	66	4.28	0.77	29.0	58	0.28	
17					46	63	63	43	17	50	3.56	0.70	28.0	101	5.37	0.94	43.0	65	1.10	
18	55	4.80	0.57	30.0	20	56	66	74	54	54	4.99	0.54	30.0	98	5.01	0.98	42.0	64	1.00	
19	38	3.23	0.59	22.5	30	66	58	47	36	39	3.30	0.59	23.0	80	5.10	0.78	38.8	90	1.10	
20	51	4.32	0.59	28.3	58	83	66	66	25	52	4.20	0.62	30.0	82	4.41	0.93	39.5	96	1.0	
										Average maximal rise in serum iron = 31										
Cases showing poor iron absorption																				

Cases showing poor iron absorption and subsequently no response to oral iron therapy but a good response to intravenous iron



GRAPH 1 —Iron absorption curves

Test dose = 18 grains ferrous sulphate given at time "0" by mouth

EXCRETION OF IRON

The iron content of the body is mainly regulated by controlled absorption. Since the use of intravenous iron therapy has become more popular, it has become a matter of great importance to know to what extent the body is able to excrete iron, since, if the body cannot dispose of excessive amounts of iron introduced into the blood stream, there is a grave danger that a condition similar to hæmochromatosis may occur.

Accordingly several experiments were carried out in an attempt to measure the excretory capacity of the body

- 1 Measurement of the normal range of urinary iron
- 2 The effect of intravenous injections of 100-300 mg Ferrivenin on the urinary and fæcal iron
- 3 The effects of oral iron therapy, transfusion and hæmolysis on the urinary iron

1 *Normal Range of Urinary Iron*—There is a wide variation in the published figures for urinary iron. Widdowson and McCance (1937) give a maximum twenty-four hour level of 0.15 mg while Barer and Fowler (1938) give a range varying from 0.8 to 1.03 mg. Because of this discrepancy of findings we carried out estimations on 50 patients who were having neither oral nor intravenous iron therapy. We found that the range lay between 0.10 and 0.40 mg with an average of 0.23 mg per twenty-four hour specimen.

2 *Effect of Intravenous Ferrivenin on Urinary and Fæcal Iron*—Nine balance experiments were carried out. This involved estimation of urinary and fæcal iron for three to four days both before and after the intravenous injection of iron. The patients were put on to a diet of known iron content. After 5 cases had been completed it was evident that the fæcal iron varied only in so far as the diet and bowel action varied and was not affected by the iron injections. This part of the investigation was therefore omitted in cases 6-9. The initial injection consisted always of 200 mg iron, but subsequent doses varied in size on two occasions. The results are shown in Table VI.

These experiments demonstrate the following features of iron excretion—

- (a) There is no apparent iron excretion into the intestinal tract
- (b) The kidneys are capable of limited iron excretion varying from 2.9 to 4.4 per cent of a 200 mgm injection
- (c) Urinary excretion of iron is not directly related to the hæmoglobin level

3 *Effect of other Conditions upon Urinary Iron*—Iron balances were carried out in patients who were receiving oral iron therapy or blood transfusions and in cases of hæmolytic anæmia and polycythæmia. In no case was there any significant elevation in the urinary iron level.

TABLE VI
Iron Balance Experiments

Urinary Iron (mg.)										Faecal Iron (mg.)		
Case	Presence of Iron Deficiency	Before Injection 3 Day Average	After Injection			Mgm Ferrivemin Injected	Per cent Dose Excreted in Urine	Daily Average			Per cent Dose Excreted in Faeces	
			1st Day	2nd Day	Average 3rd and 4th Day			3 Days Before	1st Day After	1st 3 Days After		
1	Yes	0.265	8.18	1.10	0.263	200	4.4	6.8	0	6.6	0	
2	Yes	0.22	7.20	0.38	0.21	200	3.6	10.3	15.2	8.1	0	
3	Yes	0.17	8.57	0.22	0.21	200	4.2	9.7	0	8.5	0	
4	No	0.29	8.33	0.54	0.29	200	4.2	12.4	10.5	10.2	0	
	No	0.29	11.90	1.58		300	4.3	7.5	4.25		0	
5	No	0.32	6.21	0.75	0.20	200	3.2	10.4	0	6.8	0	
	No	0.20	1.03	0.08		100	0.8	6.8	0	8.5	1.7	
6	No	0.24	8.51	0.49	0.28	200	4.3					
7	Yes	0.29	8.46	0.14	0.23	200	4.1					
8	Yes	0.20	6.07	0.18	0.19	200	2.9					
9	Yes	0.16	7.80	0.68		200	3.8					

DISCUSSION ON THE VALUE OF IRON ABSORPTION CURVES

As has been noted by Moore *et al* (1939), the factors influencing the serum iron level are not only the extent of absorption of iron from the gut, but also of red cell destruction, iron utilisation, and excretion. Nevertheless, the constancy of the present results is such that it is thought that significance may be attached to iron absorption curves provided sufficiently large quantities of iron are used as the test dose. Kooyman (1949) carried out an extensive study of iron absorption curves using 225 mg of ferrous chloride, which contains 63 mg iron or approximately 1 mg iron per kilo body weight. In our experience this dose is too small to have value and hence we consider that the dose should be approximately 4 mgm iron per kilo body weight.

A rise in serum iron of anything above 100 $\mu\text{g}/100\text{ ml}$ when the technique described above is used appears to indicate the presence of satisfactory iron absorption. From experience in the present series of experiments it is considered that most cases of hypochromic anæmia showing a rise above 100 $\mu\text{g}/100\text{ ml}$ can be expected to respond to oral iron given under supervision.

In addition to patients suffering from malabsorption there is a group with no evidence of blood loss, splenic anæmia, carcinoma, faulty diet or diarrhœa, whose serum iron curves are persistently flat (See idiopathic cases, Table I and also Table IVB). The anæmia is refractory to iron given by mouth, but responds to parenteral iron therapy. It is considered that the defect in these cases is in the absorption of iron.

CLINICAL INDICATIONS FOR INTRAVENOUS IRON

There is a limited but very definite place for parenteral iron treatment in clinical medicine. But it should be stressed that the vast majority of patients with iron-deficiency anæmia will respond to oral iron therapy, and a reasonable trial with oral preparations should be made before resorting to intravenous iron.

The indications for its use are as follows —

- 1 Persistent gastro-intestinal disturbance from taking oral iron. This is most commonly found in pregnancy and it is in these cases that we have found Ferrivenin most useful.
- 2 Malabsorption of iron due to persistent diarrhœa, steatorrhœa, gastric or small gut resection and in the rare case of idiopathic malabsorption of iron.
- 3 Rheumatoid arthritis. In this condition there is sometimes a beneficial effect on the general condition of the patient as well as on the anæmia which may be refractory to oral iron therapy.
- 4 For the rapid restoration of the body's depleted stores of iron following massive external loss of blood.

SUMMARY

1 *Iron absorption tests* were carried out in

- (a) Six normal persons
- (b) Thirty-four patients with hypochromic anæmia who subsequently responded to oral iron therapy
- (c) Five patients with hypochromic anæmia who were refractory to oral iron therapy but subsequently responded to intravenous iron

Refractoriness to oral iron therapy was related to a failure in absorption as indicated by a flat iron absorption curve

2 Investigations into the excretion of iron following intravenous iron therapy showed that none of the iron administered by this route was excreted in the fæces but that up to approximately 4 per cent of the dosage given might be excreted in the urine

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NEUROLOGICAL COMPLICATIONS OF SOME INFECTIOUS DISEASES

GWYN GRIFFITH, M D , F R C P E , D P H , D C H

Pædiatric Unit, County Hospital, Bangor

THE most interesting condition among those due to infectious diseases is the disseminated encephalomyelitis which sometimes follows, increasingly so in recent years, measles, vaccinia, whooping cough, chicken-pox and mumps

Underwood (1935) mentions the increasing incidence of central nervous system complications of infectious diseases and post-vaccinia in the previous thirty years

Henderson (1952) notes that involvement of the central nervous system has become increasingly frequent in mumps during the last forty years, and *Malamud* (1937) noted an increasing number of reports of measles encephalomyelitis. There does not appear to be general agreement about the cause of these conditions and their classification is therefore difficult. Several theories of causation are discussed at present and have been mentioned by Underwood (1935) and by Ford (1944)

- (i) Since the histological nature of the lesions seems to be essentially the same whether the condition has followed measles, vaccinia or some other illness, it has been suggested that the process is due to some neurotropic virus which becomes activated by the primary infection, or, alternatively, which invades the central nervous system when the patient's resistance is lowered by illness. The same clinical picture may develop after obscure febrile illnesses or apparently without recognisable illness. This hypothetical virus has not been demonstrated.
- (ii) Some authorities believe that the virus of the original disease actually invades the central nervous system (*Malamud*, 1937).
- (iii) Another possibility is that of demyelinating toxins produced by the virus of the original infection, and Ford (1944) considers it possible that a number of filtrable viruses may produce a series of toxins which have a similar effect on myelin.
- (iv) A suggestion, based on a study of paralysis following anti-rabies inoculation, has been put forward that the destruction of myelin, and the consequent nervous symptoms, is due to allergic reactions or the formation of antibodies.
- (v) The condition may be fortuitous.

On the whole, it may seem from the recent behaviour of those infectious diseases which affect the central nervous system that the

encephalomyelitis following an infectious disease such as, for example, varicella is due to the development of neurotropism by the virus of varicella itself

It has been noted by Underwood (1935), and recent evidence tends to corroborate that an epidemic peak occurs after epidemics of influenza and poliomyelitis

In this county the incidence of notified poliomyelitis is shown in the appended table

	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951
Poliomyelitis	6	0	0	0	2	10	0	2	29	1

In 1950 the epidemic of poliomyelitis commenced in July and reached its peak in September and waned in December. The greatest number of neurological complications of infectious disease occurred in December 1950 and January, February and March 1951 (8 cases). There was also a widespread epidemic of influenza in January 1951.

The encephalopathy associated with pertussis is striking and apparently characteristic and may be specific. It has been variously attributed to vasomotor disturbances, to air-embolism and to bacterial toxin. At present, the last-named possibility would appear to be the most attractive. It is believed that the process may cause permanent brain damage with persisting symptoms in children who survive the encephalopathy. It is possible that the lesions are analogous to the cloudy swelling of the kidneys and other viscera found in almost all acute and fatal illnesses and that they are the anatomical basis of delirium and stupor (Ford, 1944).

MEASLES

It is probable that encephalomyelitis occurs more commonly with measles than with any other infectious disease of childhood, although the incidence is low even with measles. Figures showing the incidence of encephalomyelitis in measles epidemics must be very rough approximations as the complication is rare in some epidemics and common in others.

In four relatively large epidemics in a rural area neurological complications were observed during two epidemics and no complications noted in two other epidemics. Cases occurred in small groups in such a way as to suggest an epidemic, *e.g.* in the 1947 epidemic of measles, 2 cases of severe encephalomyelitis were seen—one of whom died, and the other, although crippled, still survives.

In the 1950-51 epidemic, 6 cases were seen. Four were mild and recovery was complete. One, which was severe, has a residual paraparesis and the other has mental and personality changes. There is no obvious tendency to select either sex and the age incidence coincides with that of measles (*viz.* 1-10 years). As a rule, it is said to occur in severe cases of measles but in the cases under review, measles was

relatively mild. A number of syndromes occur, although there is, of necessity, much overlapping

- 1 Symptoms of diffuse cerebral involvement of brief duration—often termed "meningism"
- 2 Multiple focal or diffuse lesions in the nervous system
- 3 Single focal cerebral lesions
- 4 Cerebellar syndromes
- 5 Spinal syndromes
- 6 Optic neuritis
- 7 Mental and personality changes

1 *Symptoms of Diffuse Cerebral Involvement of Brief Duration (Meningism)*—The onset is usually between the fourth and fifth day of the eruption, *i.e.* at the beginning of convalescence, with drowsiness and even stupor. This may deepen into coma. Headache, vomiting, muscle twitching or convulsions follow in a few hours. Evidence of meningeal irritation is present. The course is short, and despite the alarming initial symptoms, the child is well in two or three days, but may show some irritability and lack of emotional control for several weeks. Cerebro-spinal fluid is under pressure and may show a moderate increase in cell count, globulin and total protein. Symptoms and signs point to an intoxication of the brain rather than meningeal involvement and the neck stiffness may be merely part of the generalised muscular rigidity.

The features of this group are the absence of focal signs and the quick and complete recovery. Four cases of this kind were seen during the epidemic which occurred in the first quarter of 1951. All occurred when the rash was fading and were of varying degrees of severity.

CASE REPORTS—Four cases. Two of these were in girls of 5 and 7 and were mild, showing an initial convulsion with unconsciousness for four to six hours. Bilateral extensor toes were present during this period, which was followed by a transient confusional phase. Complete recovery occurred during the following few hours.

One moderately severe case in a boy of 8 years had three separate convulsions with unconsciousness for six hours and followed by disorientation, confusion and inco-ordination for about twelve hours. Complete recovery followed.

One severe case was in a boy of 10 years who gave a history of mumps three months previously and repeated upper respiratory infections during the school year. On the fourth day of the rash he had a severe convulsion and was admitted into hospital five hours later. He had two further fits after admission. Plantar responses were extensor and tendon and superficial reflexes were not elicited. Neck stiffness, Kernig's sign, optic neuritis and a generalised muscle rigidity were present. He had one other fit on the next day and was unconscious for two days. The cerebro-spinal fluid was normal. He recovered slowly and was normal when discharged five days later and had no residual symptoms or signs when followed-up five months later. These cases were seen during January and February 1951. There was no history of migraine, epilepsy or other neuropathy in the family histories of these cases.

2 *Multiple Focal or Diffuse Lesions in the Nervous System*—

The onset is identical with the "meningism" type with similar physical signs. There is rigidity of muscle although atonia may occur. Myoclonic twitching may be present. Cranial nerve palsies are rare but the VI nerve may be involved. Paralysis of the bulbar muscles may occur and the child may die. Usually recovery begins after several days with a return of consciousness. Paraplegia and paraparesis may be found as sequelæ, but hemiplegias and monoplegias are uncommon. Pareses are as a rule spastic, but atrophic and flaccid muscles may be found. Choreic and athetoid movements have been described and speech disturbances may occur, due to bulbar palsy or cerebellar involvement or partial aphasia. Mental changes, with irritability, screaming and obscene language may be present. Sleep is usually irregular but prolonged somnolence may occur. Improvement is slow and symptoms may not disappear for years. Defects in intelligence may follow.

Ford (1928) notes complete recovery in 14 of 42 cases and 5 deaths. The remaining cases showed mental defect or personality change, disturbances of motility, epilepsy and narcolepsy.

CASE REPORT—exemplifying multiple lesions with a residual paraparesis in a girl of 3 years 7 months. She was admitted 22.5.51 with a history of a measles rash five days previously and on the day of admission she had neck rigidity, champing of the jaws, and athetoid movements of the hands and arms. Feeds were refused. She was lying supine with her eyes to the left. Extensor plantar responses and optic neuritis were present. The following day tendon reflexes were exaggerated with tremor and twitching of the arms. Two days later, tendon reflexes were absent and bilateral VI nerve weakness was present. Four days later the lower limbs were spastic. She commenced talking twenty-four days after admission and was until that time spoon-fed by the nursing staff. There was gradual improvement until her discharge from hospital six weeks after admission.

At a follow-up examination four months later, she was found to be a happy and exceedingly talkative child with a residual paraparesis not interfering considerably with walking. During this illness, meningism, involvement of the II and VI cranial nerves occurred with, possibly, some change in personality. The cerebro-spinal fluid was under slightly increased pressure, with a slight increase in lymphocytes and protein.

3 *Signs of Single Focal Cerebral Symptoms*—Hemiplegia, aphasia or hemianopia may occur in association with those symptoms already mentioned, but usually in an apoplectic fashion like a gross vascular lesion, with convulsions and coma for a time. It is probable that these cases bear a less direct relation to measles than exists in other groups of cases. They probably result from a non-specific effect on the vessel walls which may occur in any febrile illness.

CASE REPORT—A girl—the seventh of eight children, her parents and siblings were healthy and apparently normal, although her father was not of average intelligence. She was born normally on 5.5.43 and developed

normally. She suffered from convulsions with the onset of teething and thereafter at approximately three-monthly intervals. The attacks were preceded by irritability, vomiting, drowsiness and pyrexia and lasted for about three-quarters of an hour.

She was said to be a nervous and sensitive child. She had been threatened by her father that measles would follow any "wrong" action. She was admitted on 13.7.48 aged 5 years 2 months with a history of a mild attack of measles two weeks previously. She was convalescent on the fifth day and went to see a friend. She was said to have been "teased" about measles and ran home to bed. She was completely withdrawn for three days with refusal of food and no speech. Fluids had been taken for three days prior to admission. On examination, she was a withdrawn, dehydrated child with stiffness of the neck and of the left arm and left leg. No other abnormal feature was found and the C S F was normal. She continued to refuse food and developed twitching of the limbs. Parenteral fluids with calcium and vitamin D were given. She became more and more withdrawn, with occasional outbursts of obscenity and a left hemiplegia with a spasticity varying in degree from day to day. There was obvious mental deterioration which daily increased and on 3.9.46, six weeks after admission and two months after the onset of measles, she died—demented and hemiplegic. Consent for autopsy was not obtained.

4 *Cerebellar syndromes*—While purely cerebellar syndromes are apparently unusual, signs of cerebellar ataxia including loss of muscle tone, scanning speech, nystagmus, intention tremor, and typical gait may occur. These disabilities are revealed by the child's increasing activity during convalescence. Cerebellar ataxia is said to be the most striking feature of measles encephalomyelitis, and measles may be responsible for a large proportion of the so-called acute cerebellar ataxias. Skoog (1920) mentions that signs may develop gradually without other nervous manifestations.

CASE REPORT—A boy of 6 years 9 months was admitted on 21.9.47 with a history of an attack of measles in July 1947. His disability was observed in the early days of convalescence. He fell easily during attempts at walking and about a month later was noticed to be dragging his right leg and unable to use his right hand. The right plantar response was extensor and Rombergism was present. There was gradual return to normality but an ataxic gait persisted. His left arm, hand and leg were cyanosed and cold. Gradually a drooping stance and an unsteady shuffling gait became evident. There was symmetrical wasting of hands and arms, and feet and legs with poor muscle tone. In spite of attempts at re-education there has been no substantial improvement in his condition since 1948 when he was previously examined.

5 *Spinal Syndromes*—Present as an acute ascending paralysis, or a transverse myelitis, flaccid at first and then spastic although there may be atrophy of muscle groups.

Ford (1928) mentions deaths from respiratory paralysis in some patients, recovery in approximately one half of the cases and residual motor weakness of various types, including muscular atrophy, in about one-third of the cases.

6 *Optic neuritis*—Most cases show a mild optic neuritis or œdema of the optic disc

7 *Mental and Personality Changes*—Mental disturbances are not uncommon, an initial delirium having been noted in a high proportion of the cases

During convalescence, transient mental disturbances are common and prolonged toxic psychoses may occur. Fear, excitement and manic or depressive manifestations have been observed and also delirium and hallucinations, both auditory and visual. The role of the patient's personality and hereditary background is obviously a large one as there is nothing specific in the measles toxin. The commonest residuum is a reduction in intelligence. Malamud (1939) describes one hyperkinetic case with excitement and uncontrolled activity

CASE REPORT—A boy of 11 years and 4 months was first seen on 13.3.52. He was the fifth of seven children and had been born normally at full term. There was no history of intra- or neo natal anoxia and he had developed normally. He had whooping cough and chicken-pox at nine months but there was no history of convulsions. He had a mild attack of measles in March 1951. Prior to this illness he had been a quiet obedient child but gradually, following the illness, he became increasingly talkative and showed increasing and uncontrolled activity. He became unable to concentrate at school having previously been a good scholar. He had truanted on a number of occasions. There had emerged gradually a completely irresponsible type of behaviour and a lack of appreciation of his misdeeds. Over a course of months, corporal punishment and exhortations had failed to produce any result.

On examination, he was a calm, talkative boy with no evidence of organic lesion in the central nervous system. He could not deal with psychometric tests. It was discovered later that one of his siblings had been under treatment for schizophrenia. The diagnosis of nervous complications is reasonably easy with a history of measles or a fading eruption, but a case of long duration will present obvious difficulties. Poliomyelitis and tuberculosis must be considered in the initial diagnosis. The outlook is favourable and the percentage mortality is probably very low as a number of mild cases are not taken into consideration. More than half the survivors are said to show evidence of central nervous system damage.

Spastic paraplegia is the commonest residual disability and cerebellar ataxia is frequent, but some observers state that mental changes of varying degrees of severity are commonest. Mental changes are, however, usually very mild. Epilepsy is a not unusual sequel and among rare disturbances are narcolepsy and precocious menstruation with obesity (Ford and Guild, 1937).

POST-VACCINIAL ENCEPHALOMYELITIS

Attention was first drawn to this condition in 1932 although complications of vaccinia had been previously noted by Turnbull and Macintosh (1926) and Ford and Wilson (1927). Symptoms first

appear nine to eleven days after vaccination although intervals of from two to twenty-five days have been described. It may even follow unsuccessful vaccination. The onset is said to be abrupt with headache, fever and vomiting, and convulsions with meningism. Stupor and coma are said to be present and the clinical picture as a whole is similar to measles encephalomyelitis. The mortality is said to be high, but recovery in survivors is complete.

CASE REPORTS —(i) A girl aged 9 months (D O B 14 6 46) was admitted into hospital on 13 3 47. She was born normally at full term and her birth weight was 7 lbs 2 oz. She was breast-fed for three months and received adequate vitamin supplements. Eight days after vaccination in December 1946 she commenced to vomit, and showed anorexia, loss of weight, constipation, a miliarial rash, marked irritability and cough. There was some photophobia. On examination, there was no evidence of central nervous system damage. She had marked hypotonia and generalised muscle wasting and a mild respiratory infection. The heart rate was 160 per minute. There was no clinical and no radiological evidence of scurvy, rickets or primary tuberculosis. The C S F was normal and there was no evidence of urinary infection. She became increasingly stuporose and died of pneumonia seven days after admission. Consent for autopsy was not obtained.

(ii) A boy, aged 7 months was seen on 3 12 46 with a history of vaccination four weeks previously at the age of six months. On the 9th day after vaccination he developed irritability, photophobia, anorexia and a miliarial rash. Screaming attacks were described, with attempts at biting his parents and self mutilation. There was insomnia. He had a heart rate of 150 per minute and was markedly hypotonic with muscle wasting and absent tendon reflexes. Two months after the first appearance of symptoms he was almost normal, and subsequent progress was satisfactory.

(iii) A girl of 8 months, developed similar manifestations with extreme muscle wasting and hypotonia nine days after vaccination. Owing to the marked irritability and domestic unrest caused, the child was admitted into hospital. Investigations of the C N S were negative and no pathology was found elsewhere.

These three cases, eight to nine days after vaccination, showed marked irritability, anorexia, sweating, loss of weight, rash, constipation, hypotonia and muscle wasting, tachycardia and insomnia. The picture presented was similar in almost all respects to pink disease and complete recovery in the survivors did not occur for two to three months.

Turnbull and Macintosh (1926) state that it is unusual to have any residual disability although one case with persistence of spasticity for several months is described.

VARICELLA

This is a common infectious disease, but nervous complications are very rare. Bullowa and Wishik (1935) found 5 cases of encephalomyelitis in 2534 cases of varicella. Two were fatal. The onset is from three to twenty-one days after the first appearance of the eruption,

and only in rare instances do symptoms precede the eruption. Drowsiness, irritability and anorexia precede severe symptoms of vomiting, convulsions and stupor which may develop abruptly. Meningeal irritation is minimal or absent. Consciousness is regained in a few hours to days and central nervous signs become evident. Sensory loss is unusual. Spinal, cerebellar, cerebral and cranial nerve syndromes have been described. The clinical picture is almost identical with that of measles encephalomyelitis. The first British case was reported in 1914 by Miller and Davidson, who described the onset of tremor, choreiform movements, and unsteady gait in a child on the fifth day of chicken-pox. There was some disturbance of speech and difficulty in standing.

Winnicott and Gibbs (1926) noted the onset of symptoms on the eleventh day of the disease in a girl of 2 years 10 months. The symptoms included drowsiness, spastic weakness of the legs, urinary incontinence, increased tendon reflexes, bilateral Babinski response, dysphagia, dysarthria and squint. C S F was normal and recovery took place in a few weeks.

In another very small group of cases, symptoms were almost exclusively referable to the spinal cord. Smith (1926) reports a case of spastic paraplegia in a boy of 7 years with the onset in the second week of the disease and incomplete recovery in one year.

Wilson and Ford (1927) describe a case in which a boy of 3 developed spasticity on the seventh day with recovery in six weeks.

Underwood (1935) quotes 119 cases previously described and adds one case of his own. He notes the increasing frequency of nervous complications of infectious disease in the preceding thirty years, and mentions that cerebellar types are much commoner with varicella. In 107 cases there were 12 deaths and 16 others showed sequelæ of various kinds. The sex incidence in 110 cases was males 67, and females 43. He mentions that symptoms may develop before or after the eruption but more than three days before, or twenty days after, the appearance of the rash is quite exceptional. In most cases the onset is four to ten days after the first appearance of the rash.

CASE REPORT—A boy who was born on 9.10.47 was admitted into hospital on 6.6.51. He was the seventh of eight children and was born normally at full term, his birth weight being 10 lbs 4 oz. He was breast fed for two months, and according to his mother had developed normally. There was no history of convulsions. During the first week of the rash he was drowsy and vomited each day. The last scab separated one week before admission, on which day the youngest sibling was suffering from chicken pox. He was found to be unable to walk one week before admission, fell on to his knees and attempted to move about by crawling. Tremor of his hands was noticed when he attempted to feed himself and he had to be fed by his mother. On examination, he was drowsy and listless and had a fading eruption. He was unable to walk. There was a mild degree of engorgement of the right ear drum and numerous small discrete glands in the neck, axillæ and groins.

He had a mild enlargement of the liver. The cranial nerves were normal and the reflexes normal except for rather equivocal plantar responses. There was no neck stiffness. Spontaneous nystagmus, intention tremor, photophobia and marked hypotonia were present. C S F and blood count were normal and W R. was negative.

Slow improvement took place until on 15.6.51, ten days after admission, and seventeen days after the onset of symptoms, he was walking with a festinant gait and a bowed head. He was able to feed himself but had a mild intention tremor. His face was devoid of expression. On 20.6.51, three weeks after the onset of symptoms, he was standing up well but had a moderate degree of hypotonia and muscle weakness. On 18.10.51 he was walking apparently normally but was an expressionless and dull-looking boy.

WHOOPIING-COUGH

Neurological complications are, directly or indirectly, the result of pertussis. There is no evidence to incriminate a neurotropic virus. Pertussis is well known to be a more serious condition in infancy than after the age of two years. Almost all cases with neurological complications are said to occur before the age of two years. These are not uniform as in measles but include a number of entirely different manifestations.

The commonest type is characterised by the abrupt development of convulsions, most frequently at the height of the disease. Convulsions are severe, frequent and usually generalised, but may be focal. There is a high mortality and death is said normally to occur after the first convulsion. Many cases exhibit tetany, and indeed convulsions have been attributed to tetany. If death does not occur, various cerebral symptoms such as hemiplegia, monoplegia or diplegia may occur, and stupor or drowsiness may persist for a number of days. Seizures may be recurrent. The C S F. is normal or blood-stained. The lesions themselves may be due to multiple hæmorrhages or degenerative processes. Recovery may be complete.

In certain cases, the onset is insidious with drowsiness and stupor and infrequent convulsions, but with a fine twitching of the extremities (a so-called *epilepsia partialis continua* of cortical inflammation). This stage progresses into one of muscle rigidity with flexion of the arms and rigid adducted legs. Speech is commonly lost. Death may be due to a secondary infection. Convulsions or drowsiness in pertussis are evidence of encephalopathy and may lead to a dementia with generalised muscular rigidity.

Byers and Moll (1948) drew attention to a risk of the prophylactic use of pertussis vaccine which, up to that time, had not been recognised. They mention 15 instances, over a period of ten years, in which acute cerebral symptoms developed within a period of hours after administration of the vaccine. The ages varied from 5 to 15 months, and according to histories supplied by the parents, development was proceeding normally and there was no past history of convulsions. The vaccines used were made by several manufacturers. All but one

case at the time of follow-up study or death showed evidence of impairment of the central nervous system which might still have been in the healing stage in 3 or 4

During the same period about twice as many children were seen in hospital suffering from the encephalopathy complicating pertussis itself. They noted the preponderance of males and the high incidence of abnormalities of the central nervous system in the family histories. In view of the impressive evidence of the effectiveness of prophylactic pertussis immunisation now accumulating it seems likely that babies are safer immunised than not.

CASE REPORTS—(i) A girl of 2 years 1 month was admitted to hospital on 3.2.51 with whooping-cough for two weeks, having been treated at home with chloramphenicol and eumydrin. Vomiting had been particularly severe. On admission there was diarrhoea, tachypnoea and tachycardia. She had evidence of hypertelorism, a mild stupor and generalised flaccidity with continuous twitching of the hands. Calcium gluconate and calciferol were given by intramuscular injection. With increasing stupor, flaccidity and dysphagia the tendon reflexes disappeared. C.S.F. was normal with a pressure of 130 mm. Loss of speech occurred and there was continuous fine twitching of the mouth, tongue and hands. She could not take food, but as rooting and sucking reflexes were observed by accident, bottle feeding was successfully accomplished. Two weeks after admission she became more co-operative, interested in toys, parents and nurses, sitting up unaided and aware of her environment. She spoke a few words, resented bottle feeding and took a light normal diet. Two days later, there was a recurrence of partial continuous epilepsy, followed by profuse vomiting and pneumonia. Twenty-five days after admission, convulsions recurred and there was a gradual regression to a neonatal type of behaviour as shown by reappearance of rooting, sucking and tonic neck reflexes. Again there appeared a fine tremor of the hands, lips and tongue with rigid legs. Progressive deterioration was accelerated by a right hemiplegia following convulsions a few days before death. (Consent for autopsy was not obtained.)

(ii) A girl of 2 years 3 months born normally on 20.2.50. She is an only child of healthy parents with a neuropathic family history. There was no history of convulsions and no illness except whooping-cough, in November 1951. The attack of pertussis pursued a normal course, but during convalescence, her mother noticed an unsteadiness of gait and a tendency to throw the right leg out when walking. The mother compared this to the child's first attempts at walking at the age of 14 months. She had been walking quite normally for several months before the illness. When examined on 23.4.52, she was an apprehensive child who walked with a markedly unsteady gait with help. No other abnormality was noted. During the next few weeks, the ataxia increased and the child was finally unable to stand, and, owing to the tremor of her arms and hands, unable to feed herself. C.S.F. was normal.

MUMPS

Encephalitis, myelitis, peripheral neuritis and labyrinthitis have been described, but the commonest complication is probably mumps meningo-encephalitis.

Henderson (1952) notes the increasing frequency of central nervous system involvement in mumps during the last forty years. The criteria of involvement vary from observer to observer, and, quoting various authors, he shows that neurological complications vary from 1.35 to 66 per cent. In some instances the diagnosis was made on clinical grounds alone, and in others examination of the C S F provides the only evidence. Complications are more frequently seen in epidemics, and preceding or concurrent salivary gland involvement or orchitis is not necessary to the development of complications.

Kravis, Sigel and Henle (1951) state that early serologic diagnosis appears possible in about two-thirds of cases of mumps meningo-encephalitis without salivary gland involvement. In 74 patients they note predominantly meningeal signs in 62.8 per cent, encephalitic signs in 15.7 per cent and mixed signs in 21.5 per cent. Of 81 cases, 38 had no involvement of the salivary glands. Cases with and without gland involvement appear to be approximately equal. In the latter group, no clue is afforded unless there is a history of exposure to mumps or the consequent development of mumps in contacts.

In the series of 14 patients described by Henderson (1952) 11 had mild meningitis, and 4 of these 11 patients had no evidence of parotitis. In the majority of cases, vomiting, headache and feverishness are the cardinal symptoms, and common findings are drowsiness, stiffness of neck, abdominal pain and irritability. Less frequently backache and photophobia are described, and occasional instances of cerebral and cerebellar involvement have been noted.

Sequelæ are said to be rare, but Kravis, Sigel and Henle (1951) mention definite personality changes in one child three weeks after mumps meningo-encephalitis. Another child developed a left hemiparesis, a third mentally retarded child had a residual spasticity, and an 18-months-old child had ocular muscle palsy and dysphagia. Deafness, resistant to treatment, may be a sequel. All cases showed an increase in C S F protein.

CASE REPORTS —(1) A boy of 7 years was admitted into hospital on 1.12.50 with headache, backache, dysuria and feverishness. On examination there was photophobia, neck rigidity, a positive Kernig sign and an external squint of the right eye. No other abnormal feature was noted and there was gradual improvement. C S F showed 140 mgm per cent of protein, 1700 cells (50 per cent lymphocytes, 50 per cent polymorphs), increased globulin, sugar 46 mgm per cent and chlorides 730 mgm per cent. He made a complete recovery. His female sibling developed mumps one day after the boy's admission into hospital during a local mumps epidemic.

(11) A boy of 8½ years was seen on 22.10.51 with a history of meningitis in May 1949, shortly after his elder sib had developed mumps. During the attack of "meningitis" he had periods of unconsciousness for the first few days and was bedridden for one month. After this attack, his mother thought he was stupid and would take no notice of remarks and requests. He was incontinent of urine and faeces from October 1949 and was increasingly dull and backward at school. He had developed normally in infancy and early

childhood but had received a severe emotional shock by the death of his father three years previously. Psychiatric investigation showed mental defect and personality change.

CONCLUSION

The present series of cases appears to corroborate previously expressed views (Underwood, 1935, Henderson, 1952) that the incidence of neurological complications of infectious disease is on the increase. It also seems to confirm the impression that complications tend to follow an epidemic of poliomyelitis. In 1950, 29 cases of poliomyelitis were notified in the county with the peak of the epidemic in September. Neurological complications of infectious disease appeared in December 1950 and reached a peak in February 1951, a total of 8 cases having been seen during this period.

Although influenza is not a notifiable infectious disease, there was a particularly severe epidemic during January 1951. Where there is a neuropathic tendency the role of infectious diseases, particularly measles, in the ætiology of encephalomyelitis, cerebellar ataxia, and dementia in early childhood appears to be important, calling for modification of measles by gamma-globulin or convalescent human serum, in infancy and early childhood. In view of considerably greater risk of encephalopathy following whooping-cough, immunisation of the infant is desirable.

While neurological complications are, on the whole, rare, their manifestations are more harrowing and the end results often no less distressing than those of the more commonly recognised complications.

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NEW BOOKS

Book for Medical Writing By E P GORDON, M D, and W C SHEPHERD Pp viii + 112, with 26 figures London W B Saunders 1952 Price 12s 6d

This manual makes no pretence to imitate the many excellent books on English composition, grammar and style, but it aims at assisting medical writers in the preparation of their papers. It is an interesting and practical guide. First it deals with the first, second and third drafts of a paper and with the corresponding revisions, with the beginning and end of the article and with special problems. There is an excellent account of the subject of illustrations which shows how to make the most of the material available. A long chapter discusses in simple fashion statistics employed in medical papers and points out numerous pitfalls. Lastly, there are some useful appendices, including one which gives the accepted proof reader's conventional signs.

This is a curiously omnibus booklet, but very readable and full of valuable advice, and it should be studied by all who aim at making a contribution to medical literature.

A Handbook of Diseases of the Skin By H O MACKEY, FRCSI, LRCPI, DPH, LM, FRIAM Pp 216, with 36 illustrations Dublin C J Fallon 1952 Price 7s 6d net

The price of this book will appeal to students, the binding is good and the print is clear, but unfortunately the black and white illustrations fall far short of this high standard. There is a discursive section on the commonly neglected subject of Industrial Dermatitis which should prove helpful to the student, on the other hand he is not likely to appreciate the amount of space devoted to rarities at the expense of some of the common conditions. Few Dermatologists are likely to approve of the frequent recommendations to apply sulphonamide lotions and ointments. Many will be puzzled by sentences such as —“the Senear-Usher Syndrome is generally regarded as a comparatively benign type of pemphigus about 90 per cent of all cases end fatally, in a week or ten days in acute cases, in chronic cases may be over some years”.

Despite its many good points the book in its present form is unlikely to replace any of the existing “favourites”.

A Synopsis of Neurology By TATLOW, ARDIS and BICKFORD Pp 523, 84 illustrations Bristol John Wright & Sons Ltd 1952 Price 30s

This book contains much information for its size. Although synoptic in style it is easily read because of the use of many headings and variations in type. The comprehensive section on neuro-anatomy and embryology emphasises their importance in an understanding of neurology. The illustrations are good. As a means of rapid revision and reference the book fulfils its purpose admirably.

Annals of Physical Medicine Vol I, No 1 Edited by HUGH BURT Pp 36 illustrated London Headley Brothers January 1952 Single copies 6s each, Annual subscription 21s

This is the first number of a new quarterly, the official publication of the British Association of Physical Medicine (founded 1943). Physical Medicine is as old as the profession, but it is only within recent years that it has been set on a secure scientific foundation. The new journal is to include all physical agents employed in diagnosis and treatment, and will deal with rehabilitation and resettlement and include the Spas and Health Resorts.

There are two original articles in this first number. The first is a well-planned investigation into the effects of microwaves (below 30 cm). The second is an account of a simple method of dealing with the resistant complications of varicose veins. A useful feature of the journal is a collection of Abstracts of World Literature.

This new periodical should meet an urgent need, and we wish it all success.

The Neuroses By WALTER C ALVAREZ, M D Pp 667 London W B Saunders 1951 Price 50s net

This book, the product of extensive experience of the Neuroses, is written by a non-psychiatrist essentially for the benefit of non-psychiatrists. The author, Professor of Medicine, Emeritus at the Mayo Foundation, has compiled an interesting and entertaining case book. It is conveniently classified and well set out, so that a reference to almost every branch of medicine is readily available.

While the scope of the book makes it difficult to allow a profound analysis of the vast numbers of problems which the writer tackles, his observations and advice are invariably experienced and practical.

It is in no sense a textbook, rather, it may be read with profit and enjoyment by the already knowledgeable to pass the idle hour.

The excellence of the paper and printing is especially noted, within what is not now regarded as an unreasonable price.

Psychiatry in General Practice By C A H WATTS, M D, D O B S T R C O G, and B M WATTS, M B, B S Pp xiii+228 London J & A Churchill, Ltd 1952 Price 12s 6d net

This is an excellent attempt to interest the general practitioner in some of the problems concerned with the diagnosis and treatment of psychological disorders. A strong plea is made for the reorganisation of the general practitioner's time so that more attention should be given to this type of case, and it is pointed out that much time will be saved if fewer placebos are prescribed. A number of case histories are satisfactorily described so as to illustrate points at issue. The book should act as a stimulus to other general practitioners to follow in the footsteps of the Watts, and it can be recommended.

Portrait of a Surgeon John Hunter By ERNEST A GRAY Pp x+219, illustrated London Robert Hale 1952 Price 16s

The author will already be known by his earlier books—*Surgeon's Mate* and *Man Midwife*—as a sympathetic writer on medical subjects.

An excellent account is given of the life of Hunter, his work and his times, and the background is filled in with a description of the London of his day and details of his associates and pupils. Full value is given to the aims and importance of Hunter's research work. His observations forecast man's place in nature, and Darwin got much help from his publications. The basis of Hunter's tremendous amount of work is summed up in a letter to his old pupil, Jenner—"Why think? Why not try the experiment?" To John Hunter is due a great part of the advance in medical knowledge that has taken place in the past 150 years, the man "who quickened into a science the dry bones of an archaic trade."

Familiar as is the life of John Hunter to many of us, the author has succeeded in painting a portrait that will be a joy to all.

Pathology of the Fetus and the Newborn By EDITH L POTTER Pp vii+574, 601 figures London Interscience Publishers 1952 Price 150s

Dr Edith Potter has a world wide reputation and immense experience in her subject, and this remarkable book is to a large extent a record of her personal, first-hand observations. This gives it a pleasant freshness and impressive authority. It is lavishly illustrated with admirably reproduced macroscopical photographs and photomicrographs. Particularly striking are the descriptions and pictures of malformations, of which it contains an astonishing and probably unique collection. This occupies much of the book, but other aspects of the subject are not neglected, and there is much useful information about diseases and injuries, prematurity, placental pathology and various general problems. The author's interest in the clinical aspect of the subject increases the value of the book for obstetricians and pædiatricians as well as for pathologists. It is a very important contribution to the literature of foetal and neonatal pathology, and much the most complete and authoritative work on this subject at present available.

Osler—The Man and the Legend By W R BETT, M R C S, L R C P Pp vi+125, with 7 photogravures London William Heinemann 1952 Price 15s net

The author points out that Harvey Cushing's *Life of Sir William Osler* must remain the standard reference on all things Oslerian, although it fails in many ways to convey the spirit of Osler to those who knew him not. He, therefore, makes a new approach to the subject and portrays and interprets Osler in some dozen aspects which are common to him and to those to whom he is only a legend. The picture is largely built up by extracts from Osler's own writings laced together with some detail of his medical career.

One of the most striking things to which the author draws attention is the changing character of medical practice. Osler laid enormous emphasis on the study of typhoid fever and pneumonia, scourges which have largely disappeared. He prophesied that in a generation the mortality from tuberculosis would be reduced by 50 per cent. Aneurysm of the aorta, so important in his day, has become a rarity, on the other hand, a vast increase has occurred in the incidence of coronary disease. Osler said he had reached his Fellowship before he saw a case of angina pectoris, and he pointed out that in his series there were more doctors than members of any other profession, so that the disease might almost be called "morbus medicorum".

There are chapters on Osler as medical historian and classical scholar, as bibliophil, and on many other aspects of his life.

This little book is in no sense a full biography, but it does give an attractive picture of the man. It is delightfully written and exceedingly interesting, and well worth the attention of the medical profession.

Scoliosis By SAMUEL KLEINBERG, M D Pp xvi+286, with 163 illustrations London Bailliere, Tindall & Cox 1952 Price 57s 6d net

Kleinberg's textbook on Scoliosis, first published in January 1926, has now been completely re-written—and of necessity, as so many changes have taken place in many aspects of the condition. He aims to present the modern concept of the pathogenesis, to elaborate the etiology, and to review the results of modern methods of treatment.

In discussing the etiology, the author states that his careful study has revealed that 25 per cent are hereditary, and suggests it to be one's duty to inform a man or woman with scoliosis that their children may also be so afflicted. He does not say much about mensuration, because he does not believe that an involved method of graphic recording of a scoliotic deformity has any real practical value. The chapters on treatment are comprehensive and many braces and jackets are fully described, but one would like to have had more definite indication of the author's preference. In speaking of conservative treatment the author says no cure of a structural scoliosis has been reliably reported and that 10 to 20 per cent require operative treatment, from which it is suggested that in the remaining 90 to 80 per cent conservative treatment is satisfactory. Kleinberg recommends unilateral spine fusion of the Hibbs' type on the concave side with a beef bone graft to reinforce the fusion. The beef bones are obtained from the hospital kitchen. They are boiled for one hour, then cut to suitable lengths, and stored in 70 per cent alcohol where they will keep indefinitely.

This is an interesting and provocative book, but the illustrations and general production are not up to the best standards in this country.

Essentials of Neurosurgery By LESLIE C OLIVER, F R C S Pp viii+198, with 50 illustrations London H K Lewis & Co 1952 Price 25s net

This concise book is the first of its kind to be published in the country, and represents a broad survey of the present trends in neurosurgical practice. It will be of especial value to the post-graduate who has embarked upon his general surgical training and has the higher examinations before him. For the undergraduate it will form an introduction to the rapidly widening field of neurological surgery.

NEW EDITIONS

Forensic Medicine By KEITH SIMPSON, M D Second Edition Pp viii+344, with 131 illustrations London Edward Arnold & Co 1952 Price 21s

This book has the merit of comparative brevity, and the author's direct style makes it easy to read. Legal and technical aspects of the subject are dealt with only in outline, and for this there is much justification in a volume intended primarily to meet the needs of students and general practitioners. It does more than this, however, for it conveys in a precise and unequivocal manner the author's considered views on points both controversial and otherwise. These views reflect an extensive practical experience, independent thinking and sound common-sense, all of which enhance the interest and value of the book. The illustrations, with few exceptions, are very good, and the production is excellent.

Tuberculosis of Bone and Joint By G R GIRDLESTONE and E W SOMERVILLE Second Edition Pp xii+314, with 182 illustrations London Oxford University Press 1952 Price 45s net

The second edition of this well-known monograph describes the old and well-tried surgical principles of Owen Thomas and Jones for the treatment of skeletal tuberculosis. It rightly states that they are the bed rock of treatment, but it is depressing that our patients have still to look forward to such long periods on their back, though it is hoped that chemotherapy may shorten this considerably. Chemotherapy is very briefly dealt with because the authors believe it too early to judge of results. Little is said of the latest inventions, new theories, or experimental work. This can be judged in reading of the frequency of bacillæmia in human tuberculosis since the references—two—are twenty years old. Local excision of minor degrees of infection, with decompression, is used in many Clinics now under an antibiotic cover but is not mentioned here, though where a large area of bone is infiltrated wide excision is advocated, its justification being a better prognosis and a much quicker prospect of recovery.

The book, which is very well produced, forms a useful basis for study for those taking up this surgical speciality.

Emergency Surgery Part IV By HAMILTON BAILEY and NORMAN M MATHESON Sixth Edition Pp iv+193, with 311 illustrations Bristol John Wright & Sons Ltd 1952 Price 21s net

This publication continues the production in five separate parts of a new edition of this popular work. The text has been extensively revised and many of the illustrations, already a distinctive feature, have been improved.

Progress in Clinical Medicine By various authors Edited by RAYMOND DALEY, M A, M D, M R C P, and HENRY G MILLER, M D, M R C P, D P M Second Edition Pp xi+426, with 43 illustrations London Messrs J & A Churchill 1952 Price 30s

This book was first published in 1948 and its popularity necessitated a reprint in the same year. In the following three years the editors decided, in view of the rapid advances in medicine, to enlarge and rewrite the book completely, each subject remaining the work of a known authority. Wisely, the advances discussed are limited to what are now established medical and surgical practices in hospitals. The surgical contribution, especially in the fields of respiratory, neurological and psychiatric diseases, is timely, and covers ground often unfamiliar to the general physician.

To the practitioner and specialist there is no comparable work available so excellently produced at so low a cost.

The Premature Baby By V MARY CROSSE, OBE, MD, DOBSETT, RCOG
Third Edition Pp 181, with 18 illustrations London J & A Churchill
Ltd 1952 Price 16s net

The appearance of the third edition of this now well-known book is ample evidence of its popularity and acceptance as an authoritative work. It has been carefully revised and brought up to date with some additions.

Not only is the book full of detail but it also includes many useful references to the literature.

Textbook of Histology By A A MAXIMOV and W BLOOM Sixth Edition
Pp x+616, with 986 illustrations, 257 in colour on 580 figures London W B
Saunders & Co 1952 Price 50s

This edition has been extensively revised, and a new introductory chapter has been written, correlating the submicroscopic, biochemical and enzymatic constitution of cells with their structure and function. This chapter will be found most helpful to the student.

The chapter on the connective tissues has been advantageously re-arranged to include the materials dealing with inflammation and repair.

The section on the Endocrine Glands has been completely re-written and a separate chapter devoted to each gland. Many new illustrations have enhanced the value of this section.

Further important additions include forty-six new photomicrographs and several excellent illustrations by phase contrast.

The author relies chiefly on drawings for the illustrations, and it is felt that a large number of these could be replaced by photomicrographs with advantage to the student, especially if they were up to the standard of those included from the atlas of Herrath and Abramov.

The student will find this book easy to follow and very moderately priced for its size.

BOOKS RECEIVED

- Edited by MACBRYDE, CURIL MITCHELL, AB, MD, FACP Signs and
Symptoms Second Edition (Staples Press Limited, London) 70s net
- HOLZMANN, Dr MAX Clinical Electrocardiography
(Staples Press Limited, London) 105s net
- SNYDER, EUGENE F, MD From a Doctor's Heart
(Philosophical Library, New York) \$3 75
- SWIET, JOHN DE, MD (LOND), MRCP Essentials for Final Examinations in
Medicine Fourth Edition (J & A Churchill Ltd, London) 12s net
- WOLSTENHOLME, G E W, OBE, MA, MB, BCH Ciba Foundation Colloquia
on Endocrinology (J & A Churchill Ltd, London) 35s net
- Edited by BIRCH, C ALLAN, MD, FRCP Emergencies in Medical Practice
(E & S Livingstone Ltd, Edinburgh) 32s 6d net
postage 1s 1d home
- Edited by COPE, V ZACHARY, BA, MD, MS (LOND), FRCS (ENG) Medi-
cine and Pathology (Her Majesty's Stationery Office, London) 50s net
- MCLAGGAN, J DOUGLAS, CVO, FRCS, and COLLIER, JOSEPHINE, FRCS
Diseases of the Ear, Nose and Throat Second Edition
(H K Lewis & Co Ltd, London) 37s 6d net
- WILLIS, R A, MD, DSC, FRCP The Spread of Tumours in the Human
Body (Butterworth & Co (Publishers) Ltd, London) 63s net
- LAW, W ALEXANDER, OBE MD, FRCS Osteoarthritis of the Hip
(Butterworth & Co (Publishers) Ltd, London) 25s net
bv post 1s extra
- LANGDON DAVIES, JOHN Westminster Hospital 1719 1948
(John Murray, London) 21s net

Edinburgh Medical Journal

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THE INFLUENCE OF RECENT ADVANCES IN LEPROSY ON PRESENT-DAY CONCEPTIONS OF THE DISEASE IN RELATION TO ITS DIAGNOSIS, TREATMENT AND PREVENTION

By R G COCHRANE, M D, F R C P, D T M & H

INTRODUCTION

THERE may be many who consider that the emphasis which I place on recent work undertaken in Bombay unsound, for they will charge me with building up a theory on an edifice whose stability is by no means proven. I accept this charge, but I believe that the basis of this theory is logical, and proof will not be forthcoming until workers are willing to put as much time, care and patience into confirming Khanolkar's recent work as he himself has done. Others will say that leprologists have not, as yet, accepted these findings. My reply is that without the help of careful research workers in fields other than leprosy it is impossible to get a true picture of the disease. For too long leprosy has been in a compartment by itself, surrounded by an atmosphere of pity and even of sanctity, which has prevented it being viewed as an ordinary malady, the complete elucidation of which cannot be achieved without the help of scientists in all fields. Leprosy, therefore, must be studied in relation to disease processes as a whole. An explanation of related phenomena in other fields would add to our knowledge of this disease which has baffled mankind for many decades. Compassion and pity must be shown to those who are unfortunate enough to be chronically ill, but to select one disease as a particular manifestation of Divine disfavour is to distort the picture and hinder research. Disease is a manifestation of a disordered body and a disordered world, and every influence—mental, physical and spiritual—which enables a man to achieve health must in these days of enlightenment be welcomed.

An address delivered to the Edinburgh Branch of the Royal Society of Tropical Medicine, on 4th March 1952

DIAGNOSIS

The controversy as to whether the *M lepræ* is the causative organism of leprosy was sharpest in the latter part of the last century. The *M lepræ* has now been accepted as the specific cause of the disease, and this evidence has been greatly enhanced by the development of modern techniques. The latest worthy of mention are the Fite-Farraco method of staining acid-fast bacilli in the tissues, and the recent concentration method for the examination of tissue from leprosy patients devised by Khanolkar of Bombay. The former method is brought to the attention of histopathologists in staining sections for acid-fast bacilli, the latter method can be used in any well-equipped laboratory. This consists of taking a piece of tissue approximately $5 \times 3 \times 5$ mm from the selected area of skin in the person diagnosed as suffering from leprosy, placing the tissue in 3 c.c. of 1 per cent acetic acid for two to four hours. This enables the epidermis to be peeled off, leaving the corium intact.

The tissue free from the epidermis is dropped into a pyrex glass homogeniser tube with an inner ground-glass surface, in 3 c.c. of 1 per cent acetic acid. The tissue is crushed at about 2000 r.p.m. with an electrically operated mechanical glass crusher for about five to ten minutes. The crushing process is continued until a homogeneous milky emulsion of the tissue particles is obtained and a residual flake of the tough dermal tissue sinks to the bottom of the tube. The tissue particles adhering to the sides of the stirrer and the tube are washed down with about 1 to 2 c.c. of 1 per cent acetic acid, and the contents are brought to a total volume of 5 c.c. Twenty drops of petroleum ether-sulphuric ether mixture (1 in 10) are added to the turbid fluid with a drop bottle. The tube is shaken vigorously for a few minutes to ensure a thorough mixing of the tissue suspension and the ether mixture. The tube is then corked and allowed to stand in a test tube rack for about fifteen to twenty minutes.

Ten c.c. of distilled water are let into the tube along its sides for washing down any particles adhering to the wall of the tube. After about two to five minutes a white or amber coloured ring is formed on the surface which is quite distinct from the subjacent liquid. This layer contains the micro-organisms caught up by droplets of petroleum ether. Eight drops are carefully picked up from this layer with a sterile 3 mm platinum loop and deposited on a clean glass slide. The next eight drops are placed on another clean slide. The drops are then spread over an area roughly 2×2 cms. The slides are kept in a covered petri-dish to protect the smears from dust and allowed to dry in an incubator at 37°C . The dried smears are fixed by flooding the slides with Carnoy's fixative and leaving it for fifteen minutes. The fixative is then poured off and the smears are dried in air in the usual manner. Full details of this method will be published shortly. It is now possible to say that if one or other of these techniques is used acid-fast bacilli can be isolated from every active case of leprosy. I may say, in passing,

this raises the question in a more acute form of the infectivity of what has hitherto been described as non-infective leprosy. I, personally, do not believe this work alters the still generally accepted view that leprosy is only infective in those cases where bacilli can be discovered *by standard methods of examination*. To find an occasional bacillus after prolonged search, and after crushing the whole tissue, hardly justifies the opinion that the case is infective.

It is quite true that the presence of *M lepræ* is not necessary to make a diagnosis of leprosy. Nevertheless, it is always a source of satisfaction if the acid-fast organism can be detected either in sections or from the tissues. It may be asked whether these methods can be adopted in cases in which the disease has to be diagnosed where the only sign is anæsthesia, particularly in the areas of the distribution of the peripheral nerves. All that can be said is that while methods to find bacilli in such cases involve complicated techniques—e.g. nerve biopsy—any active case of anæsthetic leprosy (polyneuritic of the Havana classification) which has been studied up to the present has shown the presence of *M lepræ* either in the exudate around the nerve, or in the nerve itself.

Ever since the discovery of the *M lepræ*, and before this significant event, leprosy has been divided into two distinct types—that which has predominantly neural signs, and in which bacilli are seldom found by standard methods of examination, and that in which neural signs are less evident, and bacilli are found, frequently in large numbers.

Gradually, as the clinical picture was built up—and this was the result of patient observations of many workers—it was realised that all lesions of leprosy could be separated into those which showed a positive tissue immunity, and those in which the tissues appeared to welcome the *M lepræ* and made no attempt to check its multiplications. Thus two distinct types were differentiated—one showing a positive lepromin reaction and the other a negative one. While it is impracticable to base a classification of leprosy on immunological data alone, it is becoming apparent to an increasing number of workers that the tissue response is the clue to the understanding of the protean clinical manifestations of the disease. The diagnosis of leprosy is now no longer just a matter of whether a patient has leprosy or not, but the type of leprosy, its course, its response to therapy, or its regression with or without treatment, are factors which all have to be taken into account in the intelligent management of a case presenting itself to a physician for diagnosis.

The South American workers were the first to maintain that the lepromin test must be taken into consideration in any classification of leprosy which endeavours to be complete. These workers pointed out that all leprosy can be divided into that which shows a positive lepromin—tuberculoid or lepride—and that which shows a negative response—leproma. There has, however, been considerable confusion in the matter of the tuberculoid picture, because in addition to those lesions

which are positive to lepromin, and those which are negative, there are certain cases which show a variable lepromin. These are sometimes difficult to diagnose and classify. It is becoming increasingly accepted that this group of lesions, variously described as border-line (Wade), (Lowe), intermediate (Cochrane), dimorphous (Khanolkar), reactional tuberculoid (Schujman), and, more recently, exclusively localised macular lesions (Dharmendra), are a clinical entity whose behaviour and evolution can be predicted, and which must be included in any modern classification of the disease. The histological characters of these lesions and their immunological response were described by me some years ago. In the recent Pan-American Conference I placed before that meeting the suggestion that the classification of leprosy should be based on the immunological response of the tissues. The following is the suggested modification of previous classifications, which I feel may lead to a more logical division of the various clinical manifestations which have been described.

I am not as yet sure, but from evidence which is being collected it appears that all lesions, whether macular, infiltrated or polyneuritic,

Lepromin Positive	Lepromin Variable	Lepromin Negative
(Tuberculoid)	(Dimorphous or Intermediate)	(Leproma)
Maculo anæsthetic		Preleproma
Minor lepride	Atypical lepride	Macular leproma
Major lepride	Atypical leproma	Diffuse leproma
		Infiltrating leproma
		Nodular leproma
Polyneuritic		Polyneuritic

divide themselves into one or other of the above groups. It may be that in the dimorphous or intermediate group of cases, macular, as well as the polyneuritic lesions, will ultimately be differentiated.

For the accurate assessment and diagnosis of a case of leprosy it is inadequate simply to confirm the presence or absence of the cardinal signs of the disease—loss of sensation, tactile or thermal—nerve enlargement—or the presence of acid-fast bacilli in the tissue. In order to give a correct opinion with reference to diagnosis, response to treatment, etc., both the lepromin test and tissue biopsy, I believe, are essential. Admittedly, under conditions in the tropics, this is not possible in all cases. Nevertheless it must be accepted that without these aids one cannot be wholly satisfied that the best is being done for one's patients. Further, as experience accumulates, our clinical assessment becomes more accurate when it has been based on a long study of histopathological material from a large number of cases of leprosy. I believe that to decry these methods as time-consuming and impossible only results in a superficial judgment, and does not encourage that detailed investigation which alone stimulates scientific research into all aspects of the disease.

THERAPY

I shall now pass on to the consideration of therapy in the light of the observations which I have just made. In a recent address before the Royal Society of Tropical Medicine in London I placed before the meeting a suggestion of the method of action of the sulphone drugs. These drugs possibly act by causing the tissue environment to become unfavourable to the multiplication of *M lepræ*, and under these adverse conditions morphological changes take place in the bacilli, which become reduced to the granular form, and, over a period of two to five years or more, gradually disappear from the tissues but remain for considerably longer in the subcutaneous nerves.

There has been not a little discussion as to the active principle of the sulphone preparations, and the majority consider that all sulphones are effective in proportion to the amount of free DDS available. In other words these persons hold that there is no reason for giving complicated proprietary derivatives of DDS when all that happens is that these are changed to the parent sulphone, either in the body or by virtue of the fact that in the finished product free DDS can be demonstrated as an impurity. Others believe that the insistence on the parent sulphone being the main active agent may not altogether be true and there is growing evidence to show that di-substituted sulphones, given parenterally, are partially, and may be largely, converted into a mono-substituted derivative.

A point which is of importance, and will be dealt with in connection with the discussion on prevention, is the length of time sulphone therapy should be given. The fact that granular forms of the bacilli can be found in nerve tissue as long as eighteen months after a patient has been negative to standard methods of examination indicates that caution must be the watchword in any decision to stop sulphone therapy. Now that the generally accepted dosage of the sulphones is very much lower, it can be stated that patients should continue a maintenance dose of sulphones (1 gm of sulphetrone parenterally, or 300 mgm DDS—these dosages are given, preferably, twice weekly) for at least two years after they have been declared negative.

While it cannot be said that the sulphones satisfy the conditions of a certain specific for leprosy, the tendency to alter treatment because improvement is not rapid enough must be deprecated. It should be remembered that while the clinical response is dramatic, the bacteriological response is very slow, and only begins definitely to be seen after the second or third year of treatment. There is a place for other remedies—*e g* Thiosemicarbasone—in leprosy, but in the therapeutics of leprosy pride of place must be given to the sulphone preparations, until a better drug is discovered. Unless there is intolerance to the sulphones, treatment should not be changed, where there is manifest intolerance, particularly on low dosages, then one of the Thiosemicarbasones should be administered. There is sufficient accessible

literature to help the physician decide the form of sulphone therapy suitable to his patients in the conditions under which he is working

One matter, however, should be mentioned, and that is reaction in leprosy. This divides itself into three separate categories —

- 1 Violent local tissue response
- 2 Erythema nodosum, or acute lepra reaction
- 3 Sub-acute, or chronic, lepra reaction

The first is seen in the leprides, or tuberculoid cases. I personally believe that sulphones act in tuberculoid cases by virtue of the fact that they cause the bacilli, in the early stages, to multiply, and this sets off the trigger which results in an acute tissue response. Because of this reaction resolution of the disease is more rapid, and, thus, sulphones hasten the recovery of the patient. The speed of the recovery is in direct proportion to the intensity of the reaction. It is because of this capacity to set up reactions in the leprides that care must be taken lest increased nerve damage is produced, with resultant severe deformity. It is, therefore, sometimes advisable to excise the nerve sheath, in those cases which show gross enlargement of the nerve with œdema and tenderness, before sulphone therapy is started.

The reaction in the leprides, and to some extent in the dimorphous lesions, is an acute antigen antibody response seen locally in the tissues. Because of this localised response in tuberculoid leprosy some lesions may flare, while others are quiescent. In other words the antigen—the bacillary products—is localised in the tissue.

In the second form of reaction—erythema nodosum leprosum—the mechanism of the response is different and the approach to its control must be along other lines. This, too, is an allergic phenomena, but the antigen—bacillary products—is no longer confined to the tissues, but is circulating and as a result of the rapid multiplication of the *M lepræ* and its equally rapid destruction, a hypersensitisation arises and high fever and erythema nodosum lesions are seen. The tissues themselves are not sensitised, but there is a humoral response to the bacillary products—that is to say erythema nodosum is a type of Herxheimer reaction and comes under Stokes' definition of a toxilepid. In this connection I quote from *Fundamentals of Medical Dermatology*—"It is probable that the toxic erythemas, erythema multiforme as well as erythema nodosum in its various forms can be explained on an 'id' basis, associated with central, local or blood stream infection." The failure to understand the mechanism of these two different allergic phenomena gives rise to much confusion.

It is interesting to note that cortisone or A C T H in relatively small doses, 50 mgm per day, appears to control erythema nodosum and permits the continuance of sulphone therapy. More recent information from Lowe in West Africa, however, suggests that this form of treat-

ment should be of short duration, lest the disease itself be aggravated. The other form of reaction, where there is rapid multiplication of *M lepræ* without corresponding destruction, is much more serious and indicates the necessity for the immediate cessation of sulphone therapy, and its very gradual resumption when the acute phase has passed. In such cases even as small a dose as 25 mgm twice a week of DDS may be too great.

PREVENTION

In the light of modern knowledge of leprosy the question of control of the disease must be considered. The main basis of all control must still be the separation of infected cases from healthy persons, particularly children. The futility of complete and compulsory isolation has frequently been demonstrated. These measures arise from a primitive fear of the disease and only encourage false notions as to the infectivity of leprosy. Neither is it useful or practical to depart from the accepted opinion that the only case which is a serious public health problem is the open case. On the other hand, in our present state of knowledge, it would seem to be a serious form of wishful thinking to believe that the granular forms of the bacilli are innocuous, and dying or dead. So long as acid-fast granules can be found, the case should be classified as potentially infective. When it is realised that from the time of infection with *M lepræ* to full development of active infective lepromatous leprosy may be a matter of twenty years or more, and if, as one has seen, under sulphone therapy the lesions gradually pass through the phase of resolution back to the pre-leproma stage, it seems not unreasonable to conclude that if sulphone therapy is discontinued it may take as long a period for a relapsed case to return to the frank lepromatous type. This does not mean that sulphone therapy is not a powerful aid in controlling leprosy, it does mean that it is dangerous to rely on therapy to stem the epidemic of leprosy, and that control must be accompanied by partial, but not necessarily compulsory, segregation. Any campaign which bases its main line of attack on mass treatment by sulphone therapy, without adequate facilities for segregation of the open case, may lead to gross disappointment, and, further, the results of such facile optimism may not be seen for many years. Therefore, while encouraging the widespread use of the new and more effective sulphone remedies, which have now come within the economic reach of all, one must combat the tendency to think that victory has already been achieved. A disease which has baffled us for so many decades is not likely to be easy of ultimate control. The new and hopeful advances in our knowledge of therapy challenge us to still greater effort. It is confidently hoped that, as a result of the combined activities of the epidemiologist, the pathologist, the clinician, and the orthopædic surgeon, leprosy, ere long, will be robbed of its terror, and be yet another of the scourges of mankind which have been vanquished.

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APPLICATION OF F₉₃₃ AS A ROUTINE TEST IN SUSTAINED HYPERTENSION

By DONALD F GIBBS, M B, M R C P E

From the Royal Infirmary, Edinburgh

ONE of the less common, but important, causes of hypertension is that due to the pheochromocytoma tumour of chromaffin tissues, important in that, if left alone the tumour can produce all the devastating complications associated with a high diastolic blood pressure, whereas, if discovered, removal of the tumour offers the unusual opportunity of curing the hypertensive subject

Pheochromocytomas, although rare, may well pass unnoticed Smithwick (quoted by Goldenberg *et al*, 1947) found that in 1000 hypertensive subjects, undergoing surgical sympathectomy, inspection of the adrenal glands revealed pheochromocytomas in 0.5 per cent, since at least 15 per cent of the tumours are extra-adrenal the true incidence may well be higher, and several authors, notably Stout (1946) and Goldenberg *et al* (1947), point out that extra-adrenal pheochromocytomas are probably much more common than is generally recognised

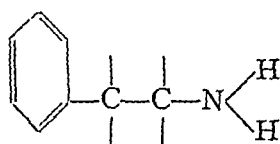
The tumours may be associated with the classical syndrome of paroxysmal hypertension, vasoconstriction, pallor, headache, tachycardia, sweating and tense feelings in the epigastrium. More commonly they present with persistent elevation of the blood pressure, indistinguishable from essential or malignant hypertension (Green, 1946) and without fluctuations of pressure (Binger and Craig, 1938, Palmer and Castleman, 1938, Philips, 1940, McCullagh and Engel, 1942, Kirschbaum and Balkin, 1942, Thorn, 1944)

Considerable amounts of adrenaline and also nor-adrenaline are produced in pheochromocytomas (Holton, 1949, Goldenberg *et al*, 1949 and 1950), but no other pressor agent has been isolated. Release of adrenaline and nor-adrenaline into the circulation can produce hypertension. At the present time the precise mechanism of the hypertension produced by pheochromocytomas is not clearly understood, although it appears to have an angiospastic basis and is generally reversible on removal of the tumour or tumours. It seems likely that excess of these pressor substances over a period of time may set up some secondary mechanism of hypertension, which is not dependent upon the continued presence of these compounds for its maintenance (Calkins *et al*, 1950, Goldenberg *et al*, 1950). The mechanism of hypertension is discussed by Calkins and Howard (1951)

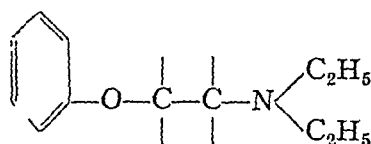
Work carried out during tenure of a Crichton Research Scholarship from the University of Edinburgh

Of the several tests suggested to simplify recognition of pheochromocytomas all can be divided into two groups. The first consists of test substances, such as histamine and mecholol, which can produce a typical paroxysmal attack, and which are especially useful in subjects whose blood pressure is within normal limits between attacks. The second group consists of agents which can block the effect of adrenaline and nor-adrenaline on the blood pressure, and which are especially valuable in those instances with sustained hypertension. The most suitable of these for clinical use is F 933 (2, 1-piperidylmethyl-1, 4-benzodioxane). Although this substance was known to have adrenolytic actions and was first investigated by Fourneau and Bovet in 1933, it was not until 1947 that Goldenberg, Snyder and Aranow described

Phenylethylamine



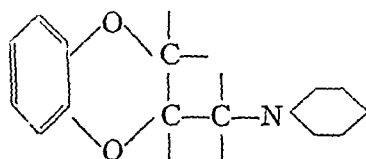
Sympathomimetic

B-Diethylaminophenetole

Adrenolytic

F 933

Piperidylmethyl Benzodioxane



Adrenolytic

FIG. 1 —The relation of F 933 to phenylethylamine

its use as a clinical test. Since then the drug has been fairly widely used in America but few reports are available in the British literature as yet.

Figure 1 shows the relationship of F 933 to a simple sympathomimetic amine known as phenylethylamine. The introduction of an oxygen atom between benzene ring and side chain results in the production of a substance with adrenolytic properties. It was suggested that F 933 accelerated adrenaline inactivation (Morison and Lissak, 1938). Competition for alcohol-amine receptors and prevention of adrenaline and like substances from combining with these receptors has been suggested by Seed and Calkins (1949).

In suitable doses of approximately 0.25 mg per kg body weight, F 933 can abolish and reverse the action of adrenaline upon the blood pressure in animals (Fourneau and Bovet, 1933, de Vleeschhouwer, 1935, Bovet and Simon, 1937) and in man (Goldenberg *et al*, 1947).

Further, F 933 can counteract the pressor effect of nor-adrenaline in man (Goldenberg, 1950) to a greater extent than in animals (Stehle and Ellsworth, 1937). At the same time it does not antagonise the action of the sympathetic system upon the blood pressure unless administered in very large doses. In addition, F 933 retains certain sympathomimetic properties such as stimulation of the central nervous system.

On the basis of these actions, Goldenberg and his colleagues suggested that if hypertension is due to excess circulating adrenaline and nor-adrenaline, then it will be abolished or significantly decreased following intravenous injection of F 933 in suitable dosage, whereas if hypertension is due to any other cause, the blood pressure will not fall following such injection. The former response of a fall in blood pressure following injection is referred to as a "positive" result, and the latter response of no fall in blood pressure as a "negative" result. During a positive response the fall in blood pressure is generally sustained for ten to twenty minutes.

A positive result in the absence of a pheochromocytoma has been reported in only one authentic instance (Dana and Calkins, 1949) and in this case a large cell neuroblastoma incorporating the left adrenal gland was found. Claim to discovery of a "false" positive case was made by Taliaferro *et al* (1949) but cannot be considered authentic. Grimson (1950) mentions a positive response in the presence of excess blood adrenaline in a uræmic subject in whom at autopsy no tumour could be found. A negative response in the presence of a pheochromocytoma is reported in 3 cases quoted by Goldenberg *et al* (1950). Mason (1951) described 2 other such cases. In such instances it is held that a secondary mechanism of hypertension has been set up. The frequency of such false negatives is impossible to assess at the moment. Thus, while a positive F 933 test almost certainly indicates the presence of one or more pheochromocytomas, a negative test does not certainly exclude a tumour.

Prunty and Swan (1950) who carried out clinical experiments similar to those of Goldenberg *et al* (1947 and 1950) concluded that the mode of action of F 933 was complex and could not be explained as a simple blockage of adrenaline like substances. Study of published work on the subject supports this view, but at the same time shows that there is evidence that F 933 is of great value in aiding recognition of pheochromocytomas as a cause of sustained hypertension, whatever its precise mechanism of action may be.

Objections have been raised to the F 933 test on the grounds of unpleasant, alarming and dangerous effects by Drill (1949) in America, and such effects are stressed in a small series of cases reported in Great Britain (Prunty and Swan, 1950, Barnett, 1950). In a patient who had had hypertensive encephalopathy, features of encephalopathy similar to those previously experienced followed injection of F 933 (Green and Peterson, 1950). Swan (1951) successfully prevented a similar occurrence with tetraethylammonium bromide. Wilkins *et al*

(1950) reported severe reactions to F 933 in 8 per cent of hypertensive patients

It is the object of this paper to describe the use of a simplified F 933 test and to comment especially upon the side effects experienced by the 400 subjects who received the drug

MATERIAL

Four hundred subjects received the standard test dose of F 933, 300 of these had sustained diastolic hypertension and of the remainder 43 had systolic hypertension associated with arteriosclerosis and a normal or slightly raised diastolic pressure, 22 subjects had thyrotoxicosis associated with a raised systolic pressure, and symptoms similar to those occurring in pheochromocytoma. Ten subjects had anxiety states and were chosen on account of their apprehensive emotional nature, the remaining 25 were normal healthy individuals at the time of the test

Of the subjects with diastolic hypertension, 10 were in the malignant phase and 6 of this group had had recent hypertensive encephalopathies, the remaining 290 subjects had "benign" hypertension and 21 of this group had an acute progressive form of the disease. Five of those in the "malignant" phase had had essential hypertension and 2 had had pre-eclamptic or eclamptic toxæmia of pregnancy, the others being probably of renal origin. One hundred and seventy-five of the "benign" cases had essential hypertension, 64 were considered to be of renal origin and another 42 had been subject to pre-eclamptic or eclamptic toxæmia of pregnancy on one or more occasions, 2 had coarctation of the aorta and 5 were myxœdematous, 1 had an auditory neuroma, but died soon after its removal and its rôle in relation to the hypertension was uncertain, 1 young man had had poliomyelitis and also a doubtful renal history

The ages of the hypertensive patients ranged from sixteen to sixty-five years, the average being forty-six years. This is lower than might be expected, but is explained in that all but 60 subjects were selected on account of the fact that they had developed diastolic hypertension at a relatively early age. 76 were males and 224 were females. The preponderance of the latter is partly related to the greater number of hospital beds available for women. Of all the subjects, 7 of the diastolic hypertensives had been in left ventricular or congestive failure as had been 16 of the arteriosclerotic group. The test was not carried out in the presence of uncontrolled cardiac failure. Twelve subjects suffered from a moderate degree of angina pectoris and 10 others had healed myocardial infarcts, more than two and less than eight months old. Six had early renal failure at the time of testing and 2 advanced renal failure

Four of the hypertensives had very labile pressures, and in 1 of these the diastolic level varied from 50 mm to 194 mm. Two of these and

3 other hypertensives had histories suggesting the "adreno-sympathetic" syndrome

Seventeen of the hypertensive subjects have since died, including 5 of the "malignant" group, and autopsy inspection of the sympathetic chain and adrenal glands was thus available. 1 subject mentioned, whose pressure was exceptionally labile, has had post-mortem examination carried out. All had "negative" F 933 responses and in none were pheochromocytomas found.

TECHNIQUE

The object of the test was carefully explained to each subject before the test began, each subject was instructed to report the onset of subjective sensations and also to note their disappearance. The test was carried out in quiet surroundings, to which the subject was accustomed. The blood pressure was estimated every two minutes over a period of twenty to forty minutes until a resting baseline was obtained with the subject lying comfortably in bed.

The drug was made up in 2 ml ampoules containing 10 mg per ml in normal saline, samples from batches were checked by the manufacturers, Messrs May and Baker, and found to contain the correct proportion of F 933. The dose administered was 10 mg per square metre body area, and this was diluted up to 10 ml in normal saline immediately prior to use, the usual dose being in the neighbourhood of 16-18 mg.

After the resting blood pressure had reached a satisfactory baseline, the test dose was injected by an assistant into a suitable arm vein. The period of injection was two minutes in each instance. During injection the blood pressure was estimated every thirty seconds and thence at minute intervals until it returned to the resting level, and then at two minute intervals for a further thirty minutes.

Within one or two days the test was repeated under the same circumstances, using 10 ml of normal saline instead of F 933, a fact of which the subject was not aware at the time. No other drugs were given at the time of the test save that phenobarbitone, $\frac{1}{2}$ gr thrice daily, had been administered before and after the test to all the hypertensive and thyrotoxic subjects.

RESULTS

1 BLOOD PRESSURE—*Hypertensive Subjects*—In no subject was there a clear "positive" response to the test. In 250 instances there was a variable rise in systolic pressure of 10-72 mm generally beginning within a minute of starting injection. The average rise was 34 mm systolic. The diastolic pressure showed no significant change in 43 of these and there was a rise of from 8-30 mm in the others, averaging 16 mm. The rise in pressure began during the injection period, reached a maximum in two to five minutes and lasted some five to twenty minutes. A typical response is shown in Fig 2.

The 8 subjects with "malignant" hypertension all had pressor responses, and these averaged 42/22 mm, which was rather greater than the average for the benign group

In 24 cases there was a transient initial drop in pressure, both systolic and diastolic, within two minutes of starting the injection and lasting no more than sixty seconds, being followed by a pressor response Fig 3 illustrates this response Both these responses indicate negative results

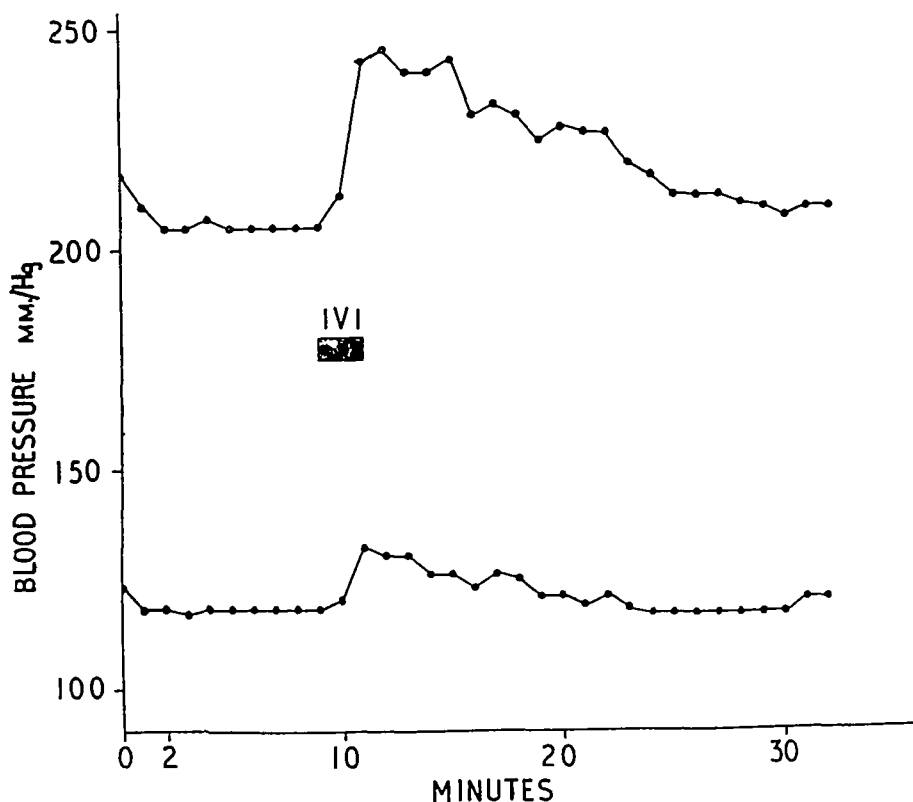


FIG 2—Patient, Mrs C A, age 62 years Benign essential hypertension F 933 test 17 5 mg I V I A typical "negative" response of blood pressure to injection of F933 in essential diastolic hypertension

In one instance (Case 127) there was a fall from 176/118 mm to 132/84 mm within a minute of commencing injection and lasting three minutes, followed by a rise to 198/122 mm (Fig 4) Repetition of the test, both in the absence of any barbiturate and one hour after administration of 3 gr of sodium luminal by intra-muscular injection, produced a similar response in each instance, the fall being from 166/114 mm to 140/92 mm followed by a rise to 212/120 mm in the former instance, and after sodium luminal from 160/118 mm to 136/90 mm followed by a rise to 200/126 mm

This patient was a woman of 61 years, with a history of headaches and dizzy turns for nine months and nocturia for "years" and with no visual upset and no tendency to sweat nor symptoms of peripheral

vasomotor disturbance Her blood pressure was 206/122 mm when first seen by the house physician in the out-patient department, but was 128/84 mm two hours later in bed twenty minutes after this a reading of 180/116 was obtained although the patient was quite quiet and at rest The first test was then performed There was moderate peripheral arteriosclerosis and grade 2 retinal changes (Keith and Wagener classification, 1939) No cardiac enlargement was present and no left ventricular hypertrophy in the multiple lead E C G Radio-

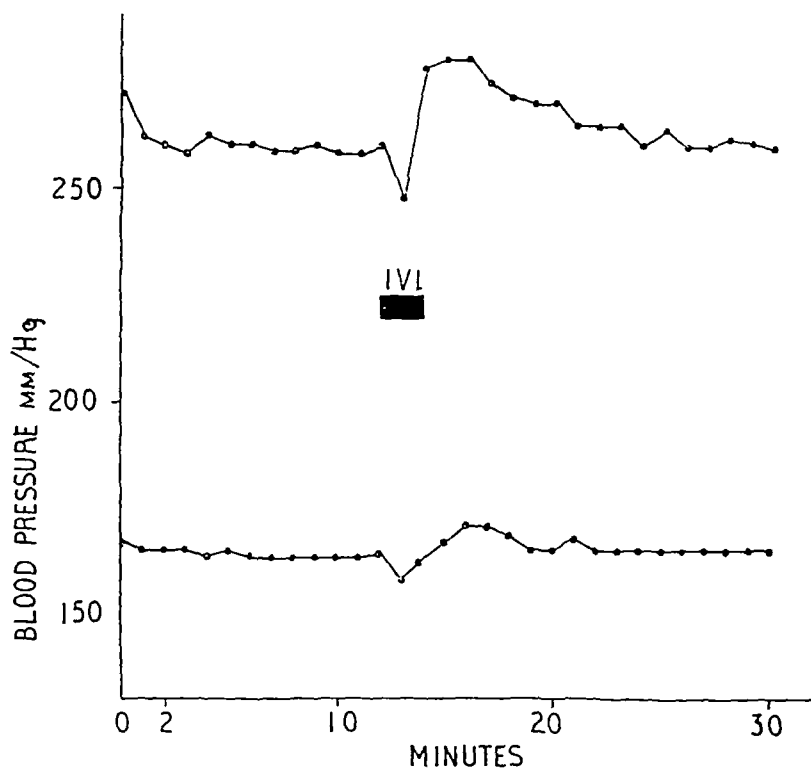


FIG 3—Patient, Mrs M G, age 32 yrs Malignant renal hypertension F 933 test 180 mg I V I The “biphasic” type of blood pressure response to injection of F 933

logically there was some aortic unfolding and the cardiac area was not significantly increased Renal function was good and intravenous pyelogram normal

The blood pressure varied at rest from 130/86 to 214/130 following I V injection of 0.3 mg hydergine it fell from 178/110 to 142/80 during the sodium amytal test it fell from 156/100 to 122/82 Response to the cold pressor test was +28/+18

Rises in pressure were not associated with symptoms of sweating or other features and were not produced by abdominal palpation No masses were found in the abdomen

At the time the test was considered to be “negative” and the

patient was discharged home. She was considered unsuitable for surgical sympathectomy, and medical treatment with adrenergic-blocking drugs or the methonium compounds was not available at the time. Unfortunately, this patient has so far refused to attend for follow-up examination. The interpretation of this response is mentioned in the discussion.

Each of the subjects presenting with a history suggesting the paroxysmal adreno-sympathetic syndrome had a clearly negative test, as did all others with labile diastolic pressures.

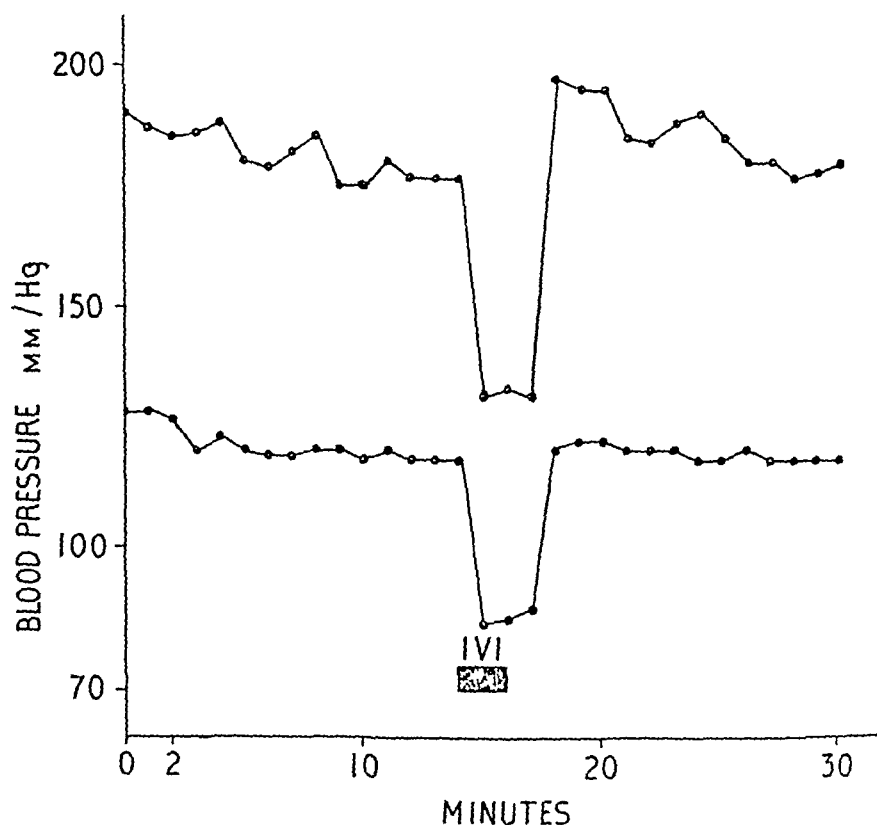


FIG. 4—Patient, Mrs R. S., age 61 yrs. F 993 test. 16.8 mg I.V.I. The blood pressure response in case 127 described in the text.

There was no relation between the ætiological agent and the type of response in the hypertensive subjects, nor was there a statistically significant relationship between the initial resting pressure and the rise in pressure.

Non-Hypertensive Subjects—Healthy normotensive subjects showed either no appreciable change in blood pressure or a mild pressor response. The greatest rise in this group was 26/22 mm and the average was 12/8 mm.

One of the thyrotoxic subjects had a transient initial fall followed by a rise in pressure, and the rest responded by a mild rise averaging 17/10 mm.

All the arteriosclerotic subjects had a rise in systolic pressure averaging 32 mm, and in 24 instances there was a diastolic rise as

well, averaging 9 mm. The 10 apprehensive subjects all showed a pressor response but not appreciably greater than the other groups, averaging 24/12 mm.

2 SIDE EFFECTS—Side effects were common but, with the exception of 3 subjects, were mild and transient, lasting no more than six minutes from the end of injection. Fig. 5 shows the type of effects recorded in the hypertensive subjects. Facial warmth, often extending to the neck and upper chest, occurred in 92 per cent and was accompanied by visible flushing of the skin in these regions in 82 per cent. Sinus tachycardia was considered to result from the test when there was a rise in heart rate of more than twenty beats per minute as compared with the saline control test. This was noticed in 70 per cent of subjects and accompanied by a feeling of palpitation in the chest in 13 per cent. A curious sighing type of respiration occurred in 68 per cent and consisted of several deep respirations usually without any increase in respiratory

F 933 Test

Incidence of side effects in 300 hypertensive subjects. Dose 10 mg per square metre body surface

Subjective—

Facial warmth	92 per cent
Palpitation	13 "
Cold or numb feelings in limbs	8 "
Apprehension	6 "
Headache	2 "

Objective—

Flushing in face or neck	82 "
Tachycardia	70 "
Sighing respiration	68 "

FIG. 5

rate, it was noticed towards the end of injection and lasted only for six to ten respirations. Cold and numb sensations in the limbs, generally the legs, were noted by 8 per cent and a feeling of apprehension and mental tension by 6 per cent but mild headache occurred in only 2 per cent.

In 3 subjects, all hypertensives, the side effects could be described as unpleasant and consisted of intense mental alarm and apprehension, together with the general subjective effects in a marked form lasting for up to ten minutes after injection and then gradually passing away over the next half hour. Each of these subjects was among the first five to receive the test dose at a time when the investigator had little idea of the expected side effects and was inwardly apprehensive, it is possible that some of this apprehension was appreciated by the patients, although when questioned later about this none could remember if it were so or not.

There was no relation between the severity of the side effects and the pressor response, nor was there a relation between the severity

of side effects and the apparent placidity or anxiety of the subject before the test. Reproduction of features of hypertensive encephalopathy in the 6 patients who had recently experienced them did not occur. No clinical features of myocardial ischæmia were produced during or after injection in the 12 subjects with moderate angina of effort, or in the 10 subjects who had infarcts of two to eight months' duration.

Only 5 subjects, including the 3 who experienced unpleasant side effects, stated they would dislike repetition of the test.

In the 25 healthy individuals side effects occurred in a mild transient form in 18 subjects and not at all in the rest. In the thyrotoxic group side effects occurred in all cases and were again mild and transient and similar to those experienced by the hypertensive subjects. The arteriosclerotic subjects behaved in a similar fashion, and in the subjects with anxiety states side effects were no more marked than in the hypertensive group although they were experienced by all 10 patients.

Response to Saline Injection—Injection of 10 ml. of normal saline was carried out two days after the test in a manner exactly similar to the test dose of F 933 and subjects were not aware of a difference in the injection material. There was no appreciable alteration of blood pressure in any group except the thyrotoxic subjects, in whom a pressor response of 10-20 mm. systolic was obtained on the average. The alterations in heart rate were not significant, and subjective effects were only noticed in 7 hypertensive and 4 thyrotoxic individuals and consisted of heavy beating in the chest in each and faint feelings in 2 of them, lasting for only a few minutes.

DISCUSSION

There exists considerable evidence that the F 933 test is of value in isolating pheochromocytomas from other causes of sustained diastolic hypertension. In some instances recognition of these tumours is impossible on clinical grounds alone.

The technique adopted for the intravenous administration of F 933 was a simple one and was satisfactory for routine use, and it evaded the necessity of erecting an intravenous drip. Particular stress is laid upon full explanation to the patient, of the purpose of the test and of what is expected of him during the test.

Especial attention was paid to the frequency and severity of the side effects during and following injection. In 99 per cent. of the hypertensive subjects and in all the non-hypertensive subjects side effects were mild and lasted less than six minutes after the end of injection. The commonest was a sensation of warmth in the face and neck, and this was often associated with visible flushing in these areas due to peripheral vasodilatation. Feelings of mental tension, sighing respirations and tachycardia are the result of the sympathomimetic action of the drug, and it is of interest in connection with the latter that pro-

duction of tachycardia is one of the few adrenaline actions in the body that is not blocked by F 933

In only 3 hypertensive subjects were side effects unpleasant, and these consisted of marked apprehension and alarm on the part of the subject, together with most of the commoner effects in an intense form. It is of interest that all these 3 subjects were amongst the first five to receive the test dose at a time when the investigator had little knowledge of the side effects to be expected and was inwardly apprehensive of the result of the test. Some of this apprehension may have made itself known to the subjects receiving the test dose.

There was no relation between the severity of the side effects and the degree of pressor response to the injection. Nor was there any apparent relation between the amount of mental tension exhibited by the individual and the severity of side effects.

In none of the 6 cases, who had had recent attacks of hypertensive encephalopathy, did features of encephalopathy occur during or after injection of F 933. Nevertheless, in view of the case reported by Green and Peterson, care should be taken when administering the drug to such subjects, and a suitable quick-acting barbiturate for intravenous injection should be at hand.

It is probable that dibenamine would be of little use in controlling encephalopathy, since it is itself prevented from sympatholytic action, by the F 933 blockade. Pentamethonium may, however, be used as suggested by Swan (1951).

It was considered unwise to employ the F 933 test in subjects in cardiac failure in view of the sympathonumetic properties of the drug, for a similar reason the drug was not administered to subjects with recent myocardial infarcts. In 12 subjects with moderate angina of effort and in 10 others with myocardial infarcts of between two and eight months of age, the test dose did not produce symptoms of myocardial ischæmia.

The side effects in the non-hypertensive group were never severe and were similar to those experienced by the hypertensive subjects, but less frequent.

The blood pressure responses were clearly negative in all but one of the hypertensive subjects. The negative pressor responses are largely the result of the increased cardiac output caused by F 933 and possibly also to a direct stimulant action of the drug on the smooth muscle of the arterioles (Nickerson, 1949). A primary adrenal medullary stimulation by F 933 is mentioned by Jourdan and Barrier (1937) but is unlikely in view of the hypotensive response in patients with pheochromocytomas. In 24 instances there was an initial transient fall in blood pressure preceding the pressor response, and this is associated with the peripheral vasodilatation which occurs, especially in muscle, following injection. Prunty and Swan (1950) describe these complex effects in some detail.

Case 127 in whom three F 933 tests were repeated and were

persistently similar, each with a significant fall in both systolic and diastolic pressures lasting three minutes, was considered negative at the time of the test. Goldenberg *et al* (1950) described a subject in whom the test was clearly positive on two occasions and similar to the response of Case 127 on another occasion. They consider that in such instances there is, at the time of the test, a sufficient amount of circulating adrenaline to "break through" the F 933 block. Experimental work has shown that, within a certain dosage range, the greater the amount of adrenaline injected, the greater the fall in blood pressure which follows a standard dose of benzodioxane (Bovet and Simon, 1937). Further increases of adrenaline concentration require increased amounts of benzodioxane to obtain adrenergic blockade (Abdon and Hammer-skjold, 1940). It is reasonable to suppose that Case 127 probably has a pheochromocytoma, unfortunately, the subject has refused all requests to return for further examination at present. The lesson to be learnt is that when this unusual response occurs the test should be repeated with a larger dose of F 933.

It would be wrong to attempt to draw conclusions about either the frequency of pheochromocytomas as a cause of sustained diastolic hypertension, or the reliability of the test in this series of 300 hypertensive subjects. Since it is known that the F 933 test does aid detection of the tumours in hypertensive subjects it is worthwhile making use of the drug as, whatever their rarity, every effort should be made to bring pheochromocytomas to light in order that they may be removed.

The purpose of this article has been to describe experience gained from practical application of the F 933 test. Results indicate that the test is simple to perform and that unpleasant side effects are most infrequent. By widespread application of the test it will be possible to ascertain its diagnostic usefulness more accurately and at the same time to obtain some further idea of the frequency of pheochromocytomas.

In view of these facts and the apparent reliability of the test to date, the drug is to be recommended as part of the routine investigation of the hypertensive subject.

SUMMARY

1 Present evidence indicates that the F 933 test is of value in aiding recognition of pheochromocytomas as a cause of sustained hypertension.

2 Three hundred subjects with sustained hypertension received an intravenous test dose of 10 mg of F 933 per square metre body surface, each dose was given over a two-minute period. Side effects were mild and transient in 99 per cent of subjects and were unpleasant in only 1 per cent of subjects. Blood pressure responses are described, and include one unusual response probably associated with a tumour.

3 One hundred normotensive individuals also received the same test dose, and in none were side effects unpleasant.

4 The test is recommended as part of the routine investigation of the hypertensive subject on the grounds of apparent reliability to date.

and rarity of severe side effects Certain contra-indications to the test are mentioned

I wish to express my gratitude to Dr A Rae Gilchrist for his advice and guidance and for permission to carry out the test on patients under his care, to Dr J K Slater for permission to use four patients in his charge, to Dr M Goldenberg of Columbia University, New York, for advice about the response of one subject, to Messrs May and Baker for supplies of F 933 and for checking the accuracy of samples, also my thanks are due to Mr Perrins for making up batches of the drug, and finally to Dr H R L Fraser for assisting in many tests

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POLIOMYELITIS

W RITCHIE RUSSELL, M D (Edin), M A (Oxon), F R C P Ed,
F R C P (Lond)

Department of Neurology, Radcliffe Infirmary, Oxford

THE poliomyelitis "scene" is changing so rapidly that it is hardly possible to keep abreast of new work. These rapid changes give reason for anxiety lest the victims of this disease may not obtain the full benefits of current knowledge. The prevalent division of responsibility for different stages of the disease must inevitably lead to inadequacies in the study of the condition. The acute stage of the disease is generally treated in a fever hospital which is often grossly understaffed, and then after three or four weeks the patient is transferred to an orthopaedic centre, where the methods of treatment adopted vary between wide extremes. There is need, therefore, for a critical survey of existing knowledge and of the attempts made to apply this knowledge to treatment.

Poliomyelitis is dependent on the invasion of the body by a virus, which is unfortunately one of the smallest known, and is invulnerable to any of the known antibiotic drugs. There are several strains of this virus, and they occur widely in both human and animal (mammalian) communities. Some of these viruses live in the human alimentary canal for long periods, and during epidemics of poliomyelitis they can be recovered from sewage. Carriers of the virus are likely to contaminate their hands, and thus spread infection to food. Further, it has been found that house flies carry the virus during epidemic seasons. In general, therefore, the spread of the virus depends on faulty hygiene.

One might have thought that with improved hygiene the disease would become less common, but unfortunately the reverse seems to be the case, for the least hygienic countries have less paralytic poliomyelitis than have their modern counterparts. The cause of this disconcerting state of affairs is not certain, but probably in the less hygienic countries the newly-born infant is first protected by transmitted immunity from the mother, and as direct infection is inevitable very soon after birth, immunity is built up safely during the early months of life. On the other hand, infants born in the relative cleanliness of modern civilisation may live for many years without developing immunity to common strains of the virus. We must therefore face the probability that a proportion of our present population of all ages have little or no immunity to poliomyelitis viruses.

The current opinion regarding poliomyelitis infection is that it is primarily an alimentary canal and systemic infection which affects a substantial proportion of the population during an epidemic, but in

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which relatively few cases of paralysis appear, and a large proportion of contacts without symptoms are found to be excreting virus in the stools

PARALYSIS AND POLIOMYELITIS

Poliomyelitis is a very minor illness in the *abortive* form, and even when meningitic symptoms develop there may be quick recovery without paralysis (*non-paralytic* form of the disease)

In the dreaded paralytic form of the disease, however, the virus exhibits some very remarkable characteristics. By far the most important of these is the unfortunate affinity of the virus for motor cells in the spinal cord (motoneurons) (Fig 1). Even in the cerebral cortex this remarkable preference of the virus for the motor cell may be very obvious, as in Fig 2, where sensory and motor cortex are both seen. This patient died about forty-eight hours after the onset of the major illness which developed during daily treatment with electric convulsion therapy. (This was a case of Dr Kelleher's, and I am indebted to Professor A. Meyer for the excellent illustrations.)

Sometimes in the acute stage there has been evidence of other tissues such as muscle being invaded by the virus, but the involvement of other cells and tissues is of relatively little importance, for tissues such as muscle can regenerate. For example, in Cocksackie Virus Infection, acute necrosis of muscle is followed by regeneration, and full recovery of the muscles concerned. On the other hand a nerve cell once destroyed can never be replaced. When there is very severe or total paralysis, over 90 per cent of the anterior horn nerve cells to the paralysed limb are found to have disappeared. In other grades of paralysis also there is a close correlation between the severity of paralysis and the number of motoneurons destroyed (Bodian, 1948).

PATHWAY OF INFECTION TO NERVE CELL

There is uncertainty as regards the route of infection to the motoneurons in the spinal cord and brain. It is generally thought that the virus must gain entrance to the body via the nose or alimentary tract (pharynx or bowel), but how it gets to the nerve cell is not fully known.

Further, the duration of the meningitic phase before paralysis develops varies within such wide limits (from about one day to two weeks) that it seems likely that the course of events as regards paralysis remains uncertain in the early part of the meningitic stage. For a time there sometimes seems to be what Sabin (1949) calls an "armed truce" between the virus and cell, and during this period the disease hovers between the allowing of complete recovery and the causing of a disastrous paralysis, in a way that is highly disconcerting to the physician.

A FEW CRITICAL HOURS OR DAYS

The liability to motor cell destruction is presumably influenced by the total dose of virus and its type and by the patient's immunological

state, but the curious uncertainties of the clinical course force attention on the possibility that the physiological state of the host and his cells plays an important role in deciding the fate of the motor cells. For example, it is known that neither the severity of symptoms nor the cerebrospinal fluid reaction in the pre-paralytic phase bears any relation to the occurrence or not of paralysis. Nor does the duration of the pre-paralytic phase bear any relation to the severity of paralysis. Yet it seems probable that the fate of tens of thousands of nerve cells is decided during a period of a few hours at a critical phase of virus activity which usually seems to correspond with the early part of the meningitic stage. We have no reason to think that any known treatment prevents the destruction of a single nerve cell after paralysis has become evident, and in many instances the fate of each nerve cell must have been decided before we see the patient.

FACTORS WHICH INFLUENCE CELL VULNERABILITY

It is now well known that viruses enter intimately into the metabolism of the host cell, so much so that the virus particles seem to disappear at certain stages of their intracellular development. Increasing attention is therefore being paid to the possibility of interfering with metabolism of the host cell. At the Second International Poliomyelitis Conference in Copenhagen (1951), Dr Horsfall stated "If the objective of interrupting virus multiplication by chemical means is to be attained, present evidence supports the idea that this will come about through substances which act on intracellular components, possibly on enzyme systems, rather than on the virus *per se*."

This field of research has been opened up very greatly by the discovery by Enders (1951) that poliomyelitis viruses can be grown on cultures of human embryonic tissues. Another promising field for research is provided by the study of bacteriophages (Delbrück, 1951) which act as viruses, in relation to the bacteria they infect. These and other fields of research are likely to increase greatly the prospects of an effective method of treatment for the acute stage of poliomyelitis, and indeed papers are already appearing which show that certain chemical substances that interfere with certain cycles in cell metabolism also delay virus multiplication.

RECOVERY OF PARALYSIS

According to Bodian's (1948) researches, the cells which are being destroyed by the virus disappear entirely in the course of a few days, as indeed may be expected from the changes seen in Fig. 1. All the other anterior horn cells, though showing chromatolysis in the acute stage, recover to a perfectly normal appearance in four or five weeks' time.

Within a month of the acute illness, the spinal cord looks normal again except that many motoneurons have disappeared. The question then arises—why do affected muscles continue to improve in strength



FIG 1a



FIG 1b

FIGS 1a and b —Section of spinal cord from a patient who died of poliomyelitis after an illness which lasted for only a few days. Nearly every anterior horn cell in the section has already been destroyed. Nissl, $\times 12$ and $\times 80$.



FIG 2a



FIG 2b

FIG 2a —The motor and sensory cortex in the same case as for FIG 1. Cell destruction in the motor cortex is very evident (2b) while the sensory cortex seems to be intact. Nissl, $\times 14$ and $\times 60$.

for so many months or even years if the surviving spinal cord cells appear normal after a month, and are presumably active again within, say, two months of the acute illness? Presumably the surviving neurones which look healthy one month after the acute illness will have much the same appearance a year later and yet the recovery of motor power is much greater at twelve months than at one month. As far as is known, nerve fibre regeneration does not occur in recovering poliomyelitis. If the anterior horn cell is only injured to a reversible extent, Wallerian degeneration does not occur in the axon, while if the cell dies there is no possibility of regeneration. There is of course no chance of nerve cells growing again, so that one can only conclude that the improved function during rehabilitation depends simply on getting the most out of the remnants of the motoneurones which survive the acute illness. There are about 12,000 spinal motoneurones supplying the nerves to each limb, and in severe paralysis of that limb over two-thirds of these (8000) may have been destroyed and cannot be replaced (Bodian, 1948).

As far as is known, the gradual improvement spread over, say, eighteen months (chiefly the first nine months) is due simply to hypertrophy of non-paralysed muscle plus the gradual enlargement and improved efficiency of surviving nerve cells and nerve fibres which seems to develop under conditions of continual stress. It is very obvious, however, from the wide variety of methods of treatment used at the present day, that the best methods of treating paretic muscles have not yet been scientifically established.

CLINICAL EVIDENCE OF FACTORS INFLUENCING CELL VULNERABILITY

It seems desirable here to refer briefly to clinical evidence that extraneous factors affecting the patient may influence the vulnerability of his motoneurones. There have, for example, been many reports of poliomyelitis following local trauma (including operation) and the paralysis developed an overwhelming preponderance in the part of the body which was involved by the injury or operation. With regard to tonsillectomy, it seems undoubted that poliomyelitis developing soon after tonsillectomy tends to involve the medulla and the dangerous bulbar type of palsy.

It has also become evident that poliomyelitis following a month of a prophylactic inoculation is liable, in a small number of cases, to lead to severe paralysis of the limb involved (Hill, 1950). Bradford Hill and Knowelden (1950) confirmed this and further found statistical evidence which suggested that inoculation not only led to maximum paralysis in the arm involved but that inoculation actually contributed to the development of paralysis in what would otherwise have presumably been asymptomatic limbs.

I have previously reported (1947, 1949) the results of a study of

questioning a series of convalescent patients with regard to their physical activity at the onset of the disease. From the figures obtained, it became evident that complete rest in bed after the onset of the major illness (meningitic stage) reduced the chances of severe paralysis to a highly significant degree, whereas there was no such correlation between the amount of physical activity taken *before* the onset of "meningitic" symptoms and the degree of paralysis. The figures were so striking as to indicate that this factor seems to play a major rôle in determining whether or not severe paralysis occurs. This view has been contested by several clinicians, but none, so far as I know, have studied the subject with sufficient care to justify an expression of opinion except Dr Horstmann (1950), and her figures were very similar to my own, as were her conclusions (Table). There is therefore a

TABLE

The Effect of Physical Activity continued after the Onset of the Major Illness, on the Development of Moderate or Severe Paralysis

	Number developing Paralysis (moderate, severe or fatal)
<i>Dr Horstmann's cases—</i>	
174 patients rested on first day of illness after onset of symptoms of major illness	62 (35 per cent)
173 patients did not rest on first day after onset of symptoms	133 (77 per cent)
<i>Dr W R Russell's cases—</i>	
38 patients rested during the whole of 24 hours following onset of major illness	8 (21 per cent)
51 patients did not rest during the whole of the 24 hours after onset	43 (84 per cent)

clear need for others to collect this kind of information so that the exact importance of this matter may be finally settled.

OUTSTANDING CLINICAL PROBLEMS

Let us now consider a few of the problems facing the physician who has to handle a possible case of poliomyelitis. The development of meningeal symptoms in any patient always raises urgent diagnostic questions, and the critical need to recognise the various forms of meningitis in their earliest stages, for treatment to be curative, greatly adds to the physician's responsibility. In poliomyelitis the wide variation in the nature and severity of the meningitic symptoms may sometimes help and sometimes hinder the diagnostic problem. For example, there might be either a painful stiffness of the neck or possibly an unbearable pain over the sacrum in a patient who otherwise feels perfectly well. On the other hand, pains in back and muscles may be severe with fever, vomiting, retention of urine and headache. In cases of spinal poliomyelitis the general mental alertness of the child is in striking contrast to the early confusion in tuberculous meningitis, but

in polio-encephalitis, loss of consciousness may be an early feature. There is no time here to consider further the differential diagnosis.

The development of meningitic symptoms causes great alarm to all concerned, and yet it is most important in poliomyelitis that the patient should be surrounded by an atmosphere of calm and efficiency. Sedation with barbiturates and analgesics should not be withheld, as restlessness and anxiety may do harm. With regard to infectivity, it is likely that several members of the house and neighbourhood are already excreting virus in the stools and are just as infective as the patient. As, however, less than one case in a hundred (in most outbreaks) develops paralysis, it is most improbable that more than one member of a small circle will develop a dangerous form of the illness, while the abortive cases will acquire a useful life-long immunity to the disease. All questions, therefore, of rushing the patient away to protect others are unreasonable in poliomyelitis, so that the physician need consider only the patient's interests in deciding whether he should go to hospital.

During epidemics the hospital beds available may be so inadequately staffed that slight cases are better nursed at home. The chief reasons for transferring cases of poliomyelitis hurriedly to hospital are (1) uncertainty regarding the diagnosis, and the special need to exclude some forms of meningitis requiring immediate treatment with antibiotics, (2) rapidly spreading paralysis which is involving the muscles of respiration to such an extent that a respirator should be at hand. Under epidemic conditions, therefore, circumstances may well develop under which small mobile squads would be useful to carry out lumbar punctures on doubtful cases, and maintain respiration if necessary while the patient is transferred to hospital.

The development of paralysis requires a reassessment of the situation, for disasters may occur very quickly. The first danger to consider is the development of difficulty in swallowing due to the bulbar type of the disease. Secretions collect in the pharynx and cause a bubbling rattle with every breath. In such cases the patient should at once be turned on his face and the foot of the bed raised two feet to allow secretions to drain out of the mouth and throat by gravity. The patient may be transferred in this posture to hospital. Mechanical aspirators (suckers) should always be available for these cases, but must be used gently. Such a patient should always be "specialed" in hospital and special training should be provided for the nurses concerned. Major errors in handling these cases are all too commonly observed. In the first place, propping up the patient makes matters worse, while putting such a patient in a respirator is generally fatal, as the machine sucks the secretions into the lungs and causes pulmonary collapse. A bulbar case should never be placed in a respirator unless the spinal muscles of respiration also become paralysed. Such cases seldom survive, but steep postural drainage should be maintained in the respirator to minimise the risk of secretions or vomit being sucked into the lungs.

The other major danger requiring prompt action is the spread of paralysis to involve the muscles of respiration. This is recognised by a quickening rate of respiration, by loss of strength to cough, by the visible feebleness of chest and diaphragm movements, and especially by the inability to say more than one or two words with each breath (tested by asking the patient to count). When respiratory power is failing, the patient becomes restless, anxious and may even appear to be hysterical. Disastrous errors in diagnosis in these circumstances are all too easy. All such cases should be transferred to a hospital experienced in respirator treatment. Unfortunately it cannot be said that the fever hospitals either in this or other countries are adequately staffed to handle these difficult problems, and there is anxiety in all countries as to the most suitable organisation for the early treatment of poliomyelitis. The doctor may be required to maintain adequate respiration during the journey to hospital. The simplest method is probably to apply intermittent positive pressure of oxygen or air to mouth and nose, and apparatus for this should soon be easily obtained in this country.

With regard to the early treatment of paretic muscles, there are some wide divergences of opinion, owing largely to the unfortunate absence of accurate physiological data regarding the pattern of muscle recovery in this disease under varying circumstances, it is to be hoped that this information will be collected by research workers before long.

Muscular fatigue is to be avoided at all costs at the onset of the pre-paralytic (major) illness, but gentle passive movements of joints should be carried out from the first day that paresis appears. The visit by a physiotherapist once a day is inadequate for this purpose, for the joints should be moved gently every few hours. It is better therefore for the nurses to receive simple instruction as to how this should be done in each case. Passive movements carried out frequently in this way prevent early contractures, spasms and joint pain, and greatly reduce the need for splinting of any kind.

The most usual treatment of partially paralysed muscle still involves prolonged rest in what is called the neutral position, with gentle assisted exercises. This traditional method of treatment has been abandoned in many clinics, and is certainly coming under highly critical scrutiny. Prolonged rest in a neutral or relaxed position may prevent or defer the development of contractures, but it also seems to delay the recovery of function in weak muscles. The quickest way to strengthen a weak muscle must always be to exercise it deliberately and frequently, but how soon this should be started and how vigorously or frequently this should be done is not known, and it may vary greatly from case to case. The following procedures show, I believe, how to investigate this problem, muscle groups can be safely used for experiment in any case of poliomyelitis, while untreated groups can be used as controls. In the first place the partially paralysed muscles can be shown to fatigue easily and recover slowly (Fig 3), and the observation of these phen-

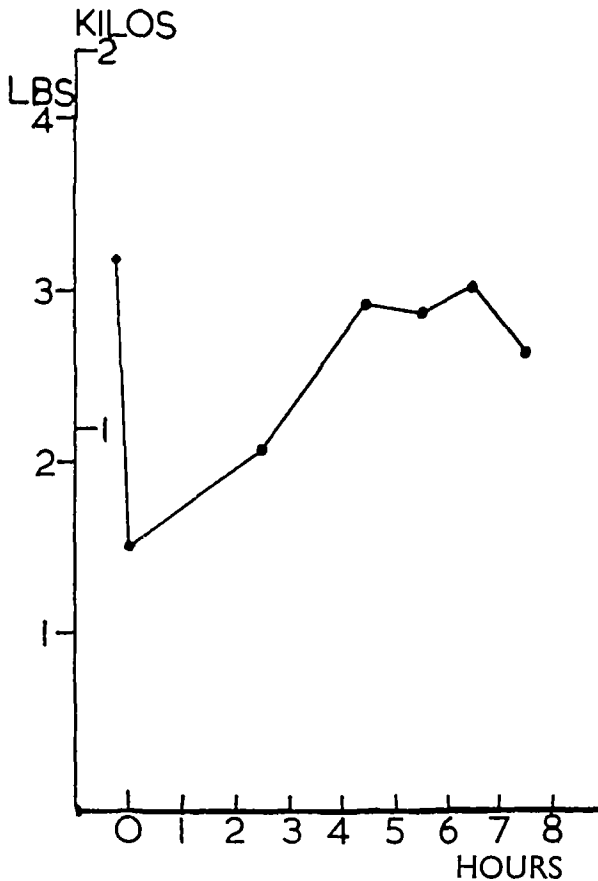


Fig 3a—Pte C *Effect of fatigue in a severely paretic triceps muscle 5 months after the acute illness* The maximum strength (measuring spring at wrist) is recorded before and after moderate fatigue. At onset the patient made a maximum contraction against resistance 6 times a minute for 10 minutes, and then 12 times a minute for a further 10 minutes. The resulting fall to half the initial strength and the ensuing slow recovery is shown.

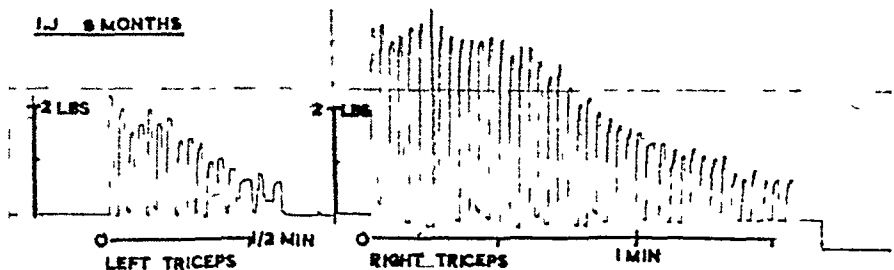


Fig 3b—Tracing on a recording dynamometer to show the rate of fatigue in the paretic muscles studied. On this occasion the patient was instructed to make repeated maximum contractions at a rate which was quick but easy to operate (see time scale).

omena has frightened people and has, I believe, had an adverse effect on the scientific development of muscle re-education. Further, the commonly used methods of recording muscle strength on the O-5 code are quite unsuitable for studying poliomyelitis. A simple spring balance is many times more accurate, as is seen in the following experiment: a patient was instructed to exhaust his paretic right triceps muscle once every hour (as in Fig 3*b*), while the work he did was measured by a simple recording ergometer. This was continued for

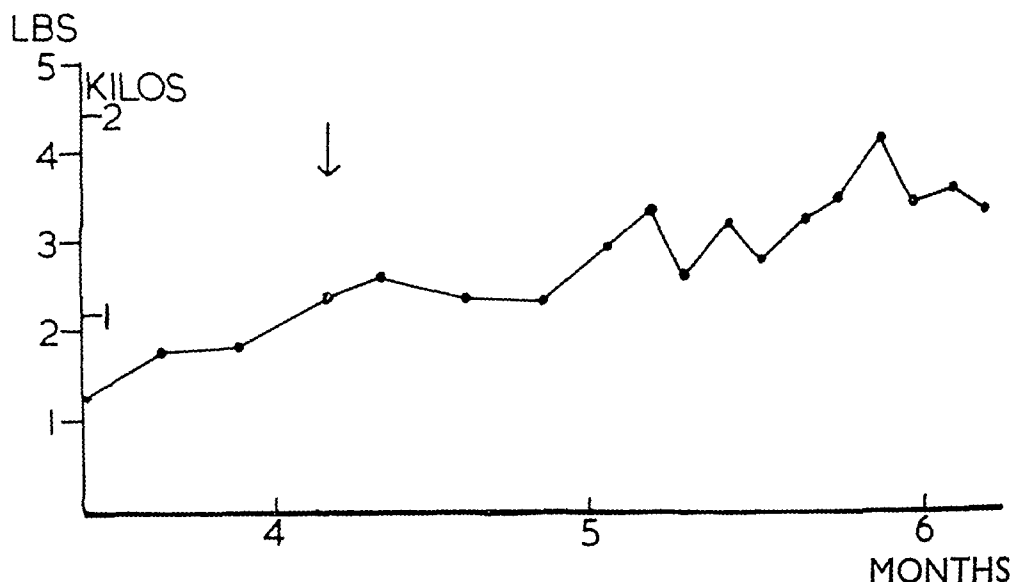


Fig 4—Pte J *Progress in strength of severely paretic muscle (triceps) submitted to fatiguing exercises. Record covers the 4th, 5th and 6th months after the acute stage.* For the first 3 weeks studied no special exercises were added to ordinary physiotherapy. Then (at arrow) repeated fatiguing exercises were started which were measured by a recording ergometer. For 3 weeks the patient exercised once an hour for 12 hours every day, continuing repeated maximum contractions on each occasion till the muscle was fatigued to the point of paralysis. This effect was produced by raising a weight of 500 g a distance of 45 cm 15 to 20 times on each occasion. After 3 weeks these hourly fatiguing exercises were carried out hourly on only 4 days each week. At this period the strength of the weak muscle was obviously increasing. Clearly the repeated and deliberately induced fatigue had done nothing but good.

several weeks, and after two to three weeks there was a considerable increase in muscle strength (Fig 4). Clearly this deliberately induced and repeated fatigue appeared to do good and certainly did no harm.

There has been a curious failure to collect such simple measurements about muscle strength at different stages in poliomyelitis, and the result is that we do not yet know the optimum plan for retraining weak muscles. There should, however, be no great difficulty in correcting this unfortunate state of affairs. After studying the theoretical aspects of the problem, and the recent American experience of robust methods of rehabilitation in polio, it seems to me very probable that within the next few years we shall see great changes in our methods of handling the stages of recovery in this country, and that these changes may

well halve the average time spent in hospital by cases of paralytic poliomyelitis

It seems necessary, however, to have a few special centres where the disease can be followed from start to finish by people experienced in studying the physiology of both muscle and nerve

Units of this type are required to determine beyond all argument what are the optimum methods of handling the acute stage of the disease, and its dangerous complications such as bulbar paralysis and respirator paralysis

They must attempt to establish the best treatment for paretic muscles at all stages of the acute and the recovery phases. They must learn to determine as soon as possible what degree of recovery is to be expected, to plan the patient's life accordingly, and to learn how soon under varying conditions it can say to the patient "to stay in hospital longer is a waste of your time"

Knowledge of the disease is progressing so rapidly that special centres are required also to study the clinical application of research on nerve cell metabolism to a degree sufficient to enable the patient to benefit from what is discovered without undue delay

Such a unit should act as instructor to other centres, and would set up a model for others to copy. It would be gratifying if Scotland were to play a leading rôle in this development

These thoughts may not seem of much importance with the incidence of poliomyelitis standing at the present low figure, but if we are likely to experience major epidemics of the disease in the future, then the more preparation we can make, the better

I am specially indebted to Dr E. H. J. Schuster, OBE, DSC, for constructing apparatus used, and to Dr J. M. K. Spalding for making the muscle records

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THE CASE FOR WIDE RESECTION IN CANCER SURGERY

By MAURICE R EWING

From the Department of Surgery, Post-graduate Medical School of London

IT seems to me that within recent years there has been manifest in surgical practice an increasing boldness in attempts to eradicate malignant disease. We can account for this more aggressive trend in a variety of ways.

First, and probably most important of all, there have become available to the surgeon, several new and immensely powerful ancillaries, such as the antibiotics, blood transfusion, better anaesthesia and the like. With their help even the average surgeon can now tackle with relative safety and with reasonable assurance, major resections, which formed earlier the rare and critical accomplishment of only the master technician. It would be surprising then, if in reply to cancer's ever-present challenge, surgeons did not re-engage in battle, this time with new weapons and with new tactics, a doughty opponent who has all too often clearly been the victor in earlier conflicts.

Second, the careful follow-up of patients and its complete analysis, has made him acutely aware of the inadequacy of our management of cancer at many sites, and has encouraged him to try to effect some improvement. There has been, for example, a keen realisation that, whereas an increasingly large proportion of patients with cancer at various sites have been surrendered almost entirely into the care of the radiotherapist, palliation rather than cure, is often the admitted objective. It is not unnatural that, especially where these results have been little better than bad, a new generation should want to try again where its predecessor has failed.

Thirdly, the surgeon has come to rely increasingly for guidance on the pathologist, who by a careful analysis of biopsy and operation specimens and of autopsy material, has made clear the inadequacy of many of our accepted operative procedures. He has also provided the surgeon with a wider and more complete knowledge of the expected behaviour of tumours at all sites, which is of immense value in planning management and in hazarding a prognosis.

It is on some aspects of this widening surgical assault on the cancer problem that I propose to comment. It seems to me that this attack has developed in a variety of different ways, which I now propose to review in turn. It will soon be evident that my separation of these various lines of development is somewhat artificial, just as it will be

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obvious that I have given a very free interpretation to what constitutes a "wide resection" in cancer surgery. When considered together, however, they can be taken to represent what we may call

THE CASE FOR WIDE RESECTION

- (1) *By electing to carry out at an earlier stage a wide operation for the removal of a tumour which the force of events is likely to compel us to do later on, even in the knowledge that, by doing so, we may be asking the patient to accept considerable deformity and disability*

A basal cell skin cancer is, in general, one of the least noxious forms of malignant disease. Failure to eradicate it at the outset, however, whether by radiation or by surgery, seems often to be the prelude to a life-long losing battle against relentless extension of the tumour. It is probably true that the incident of failure corresponds in time to the spread of the tumour to mucous membrane, to cartilage or to bone. Here it seems to establish itself with a persistent penetration that is always just ahead and just beyond repeated nibbling efforts at surgical extirpation. Of the mutilation which may result we are well aware.

I am satisfied that there comes a time in the management of such a patient when we should tackle the problem with complete ruthlessness. Timid and limited procedures cautiously practised in the hope that something less than "radical" may be adequate, are doomed to failure. We must, of necessity, do forthwith what the force of circumstance is likely to make us do later on and then with little expectation of cure.

- (2) *By the selection earlier in the disease of an operation normally reserved for the more advanced case*

We can none of us be complacent about our present efforts to cure malignant disease in the stomach. It is true that the average man's natural reluctance and the insidious character of gastric cancer, contrive together to bring very many patients to us too late for cure. But when we consider the relatively few favourable patients who survive gastric resection, undertaken in the hope of cure, we are very lucky if we salvage one in five. Nor has any alternative method of treatment presented itself which holds out any reasonable prospect of improving such a depressing state of affairs. Little wonder then, that the case is now being argued for the acceptance of total gastrectomy as the standard operation in the treatment of cancer of the stomach, omitting only growths at the cardia, which constitute a somewhat different problem.

First let us enquire what are the limitations of an adequately performed subtotal gastrectomy in the treatment of cancer of the stomach.

The incident of blood spread (57 per cent incidence of micro-

scopic vein involvement (Meissner, 1949) or of transcoelomic transfer, probably determines, at the very onset, either death or survival, so we must content ourselves with attempts to resect the local extensions of the tumour along with the regional lymph drainage area. Now, if it is true that, of patients dying from cancer of the stomach, the tumour is found at autopsy to be confined to the stomach in anything from 10 to 20 per cent (Warren, 1933, Abrams, Spiro and Goldstein, 1950) then our efforts should not be in vain.

Most of us would like to believe that we can usually keep well clear of the edge of the tumour in the stomach (always provided it is not embarrassingly large), and local recurrence in the gastric remnant does not feature large in our recollection of the disposition of post-operative recurrence. Nor are we now misled by the myth of the inviolable duodenal barrier to extension of cancer in that direction. Microscopic spread well beyond the grossly apparent outer limit of the tumour, especially in the submucous coat is, however, a feature of gastric cancer, and an error as high as one in four in estimating at operation the upper margin of the growth has been reported (Coller, Kay and McIntyre, 1941, see also Meissner, 1949, Scott and Longmire, 1949). It is true that the microscopic extension is seldom more than 4 cm beyond the edge of the tumour, as estimated naked eye at operation (Verbruggen 1931), but then 4 cm is quite a long way when resecting high up on the lesser curve. There should, therefore, be little surprise at the high incidence of local recurrence reported in the literature in recent years (Lefevre, 1947, Warren quoted by Lahey and Marshall, 1950, McNeer, Vandenberg, Donn and Bowden, 1951, Berne and Freedman, 1951, but cf Thomas, Waugh and Dockerty, 1951, Harvey, Titherington, Stout and Fordyce, 1951). This evidence certainly suggests, that when we carry out what we honestly believe to be an adequate subtotal resection for cancer, we fail to get beyond the local extension of the tumour, very often in the case of its upper margin and, not uncommonly too, in relation to its lower limit as well.

Our failure in relation to lymphatic spread is probably even more significant, when we remember that the percentage of incidence of node involvement has been computed to be as high as 88 per cent (Coller *et al*, 1941) and that, even in the absence of positive nodes, there may still be widespread infiltration of lymphatic channels in and around the stomach (Meissner, 1949). Deposits may also be encountered, not only in the obvious lymph nodes in the greater and lesser omentum but, often rather unexpectedly, at the hilum of the spleen (21 per cent, Eker, 1951), or in relation to the tail of the pancreas. Little wonder then, that in a high percentage of cases following subtotal resection the tumour first recurs in lymph nodes in the immediate vicinity of the stomach (McNeer, Vandenberg, Donn and Bowden, 1951). If it can be proved that these nodes can be more adequately removed by carrying out a total resection, then this must surely be a very strong argument in favour of the more radical procedure. And such

indeed is the inference that one can reasonably draw from recent work (Eker, 1951) where a searching examination of cleared operation specimens following total and subtotal resection, revealed in the first a significantly greater number of lymph nodes than in the second. It is, however, argued just as convincingly from the Mayo Clinic (Thomas *et al*, 1951) that by a carefully executed radical subtotal resection it is possible, and with more safety, to remove the regional lymph nodes just as widely, as by a total resection, with the exception of a small group of nodes tucked in around the cardia.

In any event, even if we admit that total resection holds out some promise of achieving a more complete local excision, and that it may even render possible a more nearly adequate removal of the area of regional lymph node metastases, can we honestly sanction it as a routine operation for gastric cancer?

Firstly, are we satisfied that, from the pathological point of view, it is a really satisfactory "en bloc" operation? I believe the answer to be "no". It fails (1) at the coeliac axis where division of the vessel is not feasible proximal to the point of origin of the left gastric artery, (2) where one must spare the hepatic artery in the right free margin of the lesser omentum, and (3) the most significant of all (and here the total operation can be no more effective than is a subtotal resection) in the inaccessible area in relation to the gastroduodenal artery and to the head of the pancreas. Little wonder then that one team of total gastrectomy enthusiasts (McNeer, Sunderland, McInnes, Vandenberg and Lawrence, 1951) is striving to extend the limits of the operation to include the body as well as the tail of the pancreas and the spleen, and the retro-peritoneal tissue below the diaphragm, this last approached through a plane of cleavage which lies behind the vascular arches of the foregut loop—a dissection which had earlier been suggested (Allison and Borrie, 1949) in relation to the more complete removal of tumours at the cardia. But even when the limits of resection are pushed thus far it still remains, from the pathological point of view, an incomplete and somewhat unsatisfactory operation.

Secondly, although in the best hands, the operation whether completed from the abdomen or from the chest or by a thoraco-abdominal approach, can be accompanied by a mortality that compares not unfavourably with that which follows a partial resection (9.5 per cent, Scott and Longmire, 1949, 5.3 per cent Walter, Gray, Priestley and Waugh, 1950, 9.4 per cent Lahey and Marshall, 1950). Can we more ordinary people reasonably expect to reproduce such good figures, or will not a prohibitive mortality and a high morbidity more than outweigh the few successes which may follow the wider resection?

Thirdly, is life after a total resection compatible with comfortable survival? On this issue there is widely conflicting evidence, and, in its evaluation, I have no personal experience to guide me. It is clear that a diminished capacity to take food in any great amount, and distressing symptoms of "dumping," go hand in hand with failure to gain weight—

an old man in poor circumstances can come near to death from starvation. Add to that the risks of dysphagia, diarrhoea, vitamin deficiency and anæmia, and it is apparent that, although there is a minority who can apparently return to full productive capacity in a tolerably good state of health (Farris, Ransom and Coller, 1943, Smith, 1947), life for the remainder often continues to be one of sem-invalidism (Stammers and Brain, 1951).

Fourthly, does the more extensive operation offer a better chance of cure? This question is as yet unanswered. It is still the standard practice, in this country at least, to reserve the total operation for the worst cases, with a massive tumour, for the removal of which a subtotal resection would obviously be inadequate, or for the uncommon linitis plastica (Pack, McNeer and Booher, 1947). The results following its use under such circumstances are bound to be bad. However, active canvassing (and, surprisingly enough, by even such a cautious campaigner as Lahey (Lahey, 1950) has, in the American continent converted a not inconsiderable body of surgical opinion to advocating total resection as the standard procedure for even the early case—what has been called (Lefèvre and Lortat-Jacob, 1950) “la gastrectomie totale de principe” in contrast to “la gastrectomie totale de nécessité”—the standard total resection of our experience from which, alone, we tend to judge the merits of this operation. Now the success of the Miles operation for rectal cancer (and its less important limitations too) lies in its completeness for a lesion at any site, and in his insistence on its practice for the smallest and most favourable tumour. It may well be that total gastrectomy may similarly come to earn a dividend, when it is applied routinely, as the operation of choice for every gastric cancer, however small. It is, however, right, I believe, that there should be some reluctance to exchange the relative safety of suturing even a tiny gastric remnant with a firm peritoneal coat, for the uncertainty of an œsophago-jejunal anastomosis (Thomas *et al*, 1951). Perhaps we should be intent rather on extending the scope of the operation only in the direction in which the site of the tumour suggests that spread would be most likely (Harvey *et al*, 1951). Unfortunately, here again the evidence of pathology affords us no encouragement since several workers have found little correspondence between the site of the primary and the direction of the main line of lymph node involvement (Coller *et al*, 1941, Meissner, 1949, Eker, 1951).

It may well be, that in the coming years we shall have news of encouraging improvement in the results following total gastrectomy, but, so far as I am aware, there has been as yet no published reports of an extended trial of total gastrectomy as the operation of election in all resectable stomach cancers. We should, I feel sure, make trials of this operation, but I am all for embarking on such efforts with a healthy scepticism, and I am not encouraged to expect any real improvement in the outlook of a patient with cancer of the stomach as the result of such an enterprise.

(3) *By extension of the principle of the "en bloc" operation*

The ideal cancer operation at any site is the "en bloc" resection of the primary along with the adjoining tissue up to and including the regional lymph nodes. In the colon and rectum, for example, this has been established as the standard practice, and within recent times there have been many attempts to devise similar operations at other sites.

One interesting development of this type has been the elaboration of operative techniques to allow of a comparable resection of the more accessible mouth cancers. Most of this work has been carried out in the United States, and several papers have appeared in recent years describing a variety of surgical procedures of this type (Sugarbaker and Gilford, 1946, Slaughter, Roeser and Smejkal, 1949, Edgerton, 1951, Ward and Robben, 1951, Kremen, 1951, Carroll, 1952). An increasing dissatisfaction with the results of radiation therapy has largely stimulated this interest, and, even in clinics where surgical methods have been regarded with some favour, the practice of treating the primary and the cervical lymphatic network, as quite distinct and separate problems, has never seemed to be in accord with the evidence of pathology. There has also been a not unreasonable feeling that, bearing in mind the infrequent but still quite remarkable success achieved years ago by men like Butlin and Trotter, it is high time for us to re-evaluate the results of surgery in this field. Having seen something of this type of work in the Memorial Hospital in New York, I am satisfied that such methods of surgical treatment are well worth a trial. It is true that an excision which involves dissection of the neck nodes is a formidable one, but the mortality of such procedures, even in the old poor-risk subject, is much less than that which follows an abdominal operation of corresponding magnitude. Usually it is necessary to resect the intervening jaw to improve access and to facilitate closure. But even in these patients the morbidity is astonishingly low, always provided an adequate airway is maintained in the early post-operative period by tracheostomy, a good nutrition is assured by generous diet given through an oesophageal tube and fistula formation prevented by a meticulous multi-layer closure. Lesions of the tongue, floor of mouth, alveolus, lip, and even the anterior pillar can be dealt with in this way, and precisely the same principles are applicable at other sites in the neck, as, for example, in removal of a malignant tumour of the parotid, larynx or thyroid, always in continuity with a neck dissection. Nor is the functional disability which follows other than acceptable in the vast majority of cases, early troubles with mastication can be overcome with the help of a high protein sloppy diet, and articulation is as a rule only slightly impaired. In the successful cases no doubt plastic reconstruction can be entertained, but I would counsel due caution before embarking on any ambitious repair.

With some slight hesitation I would like at this point to say something of malignant melanoma, in some ways the most tragic of all

malignant tumours, occurring, as it does so often, in the young and healthy, with such sinister and fatal development, from such trivial and insignificant beginnings. Although the "en bloc" operation first suggested by Hogarth Pringle (1908) goes some way towards satisfying the requirements of observed pathological behaviour, only too often there is the disappointment of local recurrence or of metastases, somewhere between the primary lesion and the proximally situated nodes. For such a highly lethal disease might there not be the strongest argument in favour of the most radical and mutilating surgery, for even a fore- or hind-quarter amputation, for lesions on the extremities (Pack and Ehrlich, 1946, Bowers, 1949, Pack, 1951)? We turn from such a suggestion with abhorrence, certainly as a primary operation. Firstly, because it seems so unreasonable to remove so much, for what may be a minute primary lesion, secondly, because we cannot be certain that by even such a devastating operation we are going to improve materially the prospect of survival, and thirdly, because we fear that a less radical operation might by chance achieve a cure. But it may be, that we should turn to any measure which holds out any promise of bettering the present five-year survival rate of 28 per cent (Wright, 1949). The same argument might be used in relation to malignant synovioma, which has a predilection unusual among mesodermal tumours, to metastasise by the lymph stream. It is true that such few reports as are available about fore- and hind-quarter amputation for these two very grave forms of cancer are very far from being encouraging, but then they have been tried in almost every instance only as a last resort.

(4) *By a wider resection where we have pathological evidence which suggests that only by so doing can we make the operation complete*

There has been evident dissatisfaction within recent years with the standard operation for the resection for left colon cancer. A high proportion of C2 (Dukes) cases and, in general, poorer results than follow right hemicolectomy (although this is not evident in every series, *e.g.* Welch and Giddings, 1951) have led to efforts to render more complete the resection of the lymph node-bearing area. Such attempts necessarily involve more proximal ligation of the main arteries. For example, in the case of a tumour on the summit of the sigmoid loop, division of the inferior mesenteric at its point of origin renders obligatory an anastomosis well below the level of the peritoneal reflection, at a point where the viability of the rectal stump is dependent on blood supplied by the middle and inferior rectal vessels (Welch *et al*, 1951, Deddish, 1950 (b), Gilchrist, 1950). A complete operation for the resection of the extra-peritoneal rectum would similarly make necessary a mobilisation of the splenic flexure to allow its delivery in the lower abdomen as a terminal colostomy. It is true that a resection of this type is somewhat more formidable than is our usually more restricted removal. Even if we are unwilling to accept this as our standard pro-

cedure, however, there would certainly seem to be every justification for such an operation when there is evidence of involvement of the lymph nodes at or above the customary point of vascular ligation. In support of a wide resection of the mesocolon, there is the additional argument that spread along the gut to adjoining paracolic nodes has been noted to occur in a very high proportion of cases, where there is a diffuse infiltration of the more proximally situated lymphatics (Grinnell, 1950).

Energetic attempts are now being made to extend the limit of the abdomino-perineal resection to include the para-aortic chain of nodes, on one or on both sides, as well as to make a complete clearance of the node-bearing tissue in relation to the main vessels of the pelvis and to the adjoining viscera (Deddish, 1950 (a)). A 16 per cent involvement of nodes not normally included in the routine Miles resection has been reported, a figure which rose to 24 per cent when only advanced cases were considered (Deddish, 1951).

Some recent work in relation to the significance of adhesions discovered at operation for the resection of colon and rectal cancer has also some bearing on the extent of the excision necessary to achieve cure. When we are confronted by a cancer of colon which is attached across the peritoneum to an adjoining viscus, we are often tempted to regard it, too hopefully, as due probably to an inflammatory cause, and acting on this assumption to separate the two by blunt dissection. It seems that adhesions of this type are seldom due entirely to inflammatory causes, it is always wise to assume that under such circumstances the cancer has already penetrated at least as far as the serous coat (Sugarbaker, 1946, Sugarbaker and Wiley, 1950).

- (5) *By pushing to the limit the extent of surgical excision where we have every reason to hope that there is only wide local infiltration without distant spread*

Surgery of this sort is bound to have many disappointments but even the most heroic procedures are justified at certain sites. Chief among them is cancer in the colon, and we must all number in our experience happy survivals after extensive operations which have involved removal of segments of adjacent bowel, abdominal wall, bladder, liver and the like. These are the tumours which, proudly mounted in bottles, largely go to furnish impressive trophies in our surgical pathology museums. Even in the presence of widely infiltrating local extension of the disease there may still be minimal lymph node involvement (Sugarbaker and Wiley, 1950), and we must never be dismayed either by the size of the primary, or by the magnitude of the dissection required for its removal.

Following the lead of Brunschwig (1948, 1949) wide resections are now being employed in attempts to eradicate infiltrating pelvic tumours, whether primarily in the female genitals or in the bladder or rectum. The technical problems involved are, however, much more formidable

than is commonly the case with colon and rectal growths, and the difficulties of safely diverting the urinary stream cannot yet be said to have been satisfactorily resolved (Bricker, 1950)

Similar wide local removal is justified for the well-differentiated accessible cancers of the mouth which may be astonishingly late in metastasising to regional nodes

(6) *By a planned attack on recurrent disease*

Wangensteen (1949, 1950) has in recent years become the exponent of what he calls the "second look" a conception of extended cancer surgery which, so far as I am aware, is primarily his own. Experience led him to believe that there is often, in the natural development of recurrent cancer, a long and insidious period of latent growth before it becomes clinically obvious. He has further been impressed by the ease with which persisting or recurring cancer can often be removed surgically. These two beliefs have encouraged him, in the case of cancer of the colon, where at the primary resection there was histological evidence of regional lymph node involvement, to counsel a "second look" four to six months later. This is an exploratory laparotomy carried out in spite of a complete lack of symptoms. If cancer is still present and lends itself to excision, a second or even a third or fourth "second" look becomes obligatory at intervals of six months, maybe each time in the complete absence of any symptoms, until a negative exploration suggests that further searching is no longer necessary. Any reluctance on the part of the patient to submit to further exploration is apparently overcome by a frank statement of the threat to life from possible persisting cancer. He has as yet published little on the results of such a campaign, and the story of his first case impresses one more by the undoubted courage of his long-suffering patient than by the wisdom of the method itself. For my own part, I am not satisfied that one knows enough about the natural history of persisting cancer in the abdomen untreated, to assess the real value of this plan of treatment. In any event, I would find it difficult, in the complete absence of all symptoms, to press with any firm conviction for a further laparotomy.

(7) *By an obstinate refusal to admit defeat when confronted by a recurrence*

I think it may well be that if Wangensteen has so far failed to convert many surgeons to the philosophy of the second look, his enthusiasm has encouraged not a few to be more venturesome in the management of suspected or of overt recurrence.

There must be many cases now on record where the disappointment of discovering a local recurrence at the site of anastomosis following an anterior resection for a rectal cancer has not deterred the surgeon from carrying out later an abdomino-perineal resection with every expectation of ultimate cure (Goligher, Dukes, Bussey, 1950).

It was Alexander and Haight (1947) who first made it clear that,

under certain conditions, a reasonable case can be stated for the resection either by lobectomy or by the segmental method of a secondary deposit in the lung. For example, the primary must be controlled and the secondary be, not only solitary, but strictly confined to the lung parenchyma. The histology of the tumour is obviously highly significant in guiding the selection of the suitable case and of the relatively small number dealt with in this way to date (Seiler, Clagett and McDonald, 1950), colonic adenocarcinoma has been the commonest tumour with hypernephroma and fibrosarcoma as less frequent alternatives. In general, the longer the interval between the resection of the primary and the first appearance of the secondary, the more one should be encouraged to go ahead in the belief that the slowness of development in the recurrence points to a high natural resistance on the part of the host (Dunphy, 1950).

- (8) *By a refusal to regard with abhorrence any surgical excision however devastating which is conceived and executed with the sole object of achieving cure*

I would regard this as a somewhat dangerous philosophy more in keeping with what one has heard of surgical method in Germany in bye-gone days than with the more cautious approach so characteristic of our own race. On the other hand, one must admit that our native squeamishness is not always in the best interest of our patients, and I should never exchange an extensive operation, for any less satisfactory method of treatment, just because it seems an easier way out. The sentiments which have encouraged the dangerous practice of anterior resection, to avoid colostomy, are engendered by somewhat similar considerations.

- (9) *By extending the scope of the operation for cure where the results of present treatment have proved to be disappointing*

Each year carcinoma of the breast claims in England and Wales alone just over 7000 victims of whom roughly one in five is under the age of forty-five. This is a disturbing record for it is not a new and unfamiliar disease, and is, at the outset, almost a superficial tumour as readily accessible to the surgeon's knife as to the patient's palpating hand. We blame patients for coming too late, when the disease is already too far advanced, but we fail at the same time to campaign vigorously for earlier diagnosis. And we do worse than that, or so, at least it seems to me. As I recollect, the management of breast cancer was no problem when I was a house surgeon in the Royal Infirmary fifteen years ago. Operation "when feasible" was the rule, and the criterion of "feasibility" depended largely on the enterprise or lack of it in the surgeon, or alternatively on his good judgment or the reverse, which is a more charitable and probably a more accurate way of expressing it. Time may well prove that the "Edinburgh method" of treatment so widely held with so little regard, is nearer the solution that is present

orthodox practice, but be that as it may, its introduction by McWhirter (1948) has had, I believe, the infinite merit of disturbing, in some degree, the shocking complacency with which most surgeons regard the present management of breast cancer. For even in the favourable group—the clinical Stage I—when there are no detectable axillary metastases, even the best salvage rate is 80 per cent. It is true that often the patient's fate has already been determined by the accident of venous spread, in the face of which, even the most radical resection is so inadequate. It is also true that, when in the review of Stage I operation material, a pathologist, even the most conscientious, reports freedom of axillary node involvement, the painstaking cutting of serial sections may unmask a diagnostic error as high as $33\frac{1}{3}$ per cent (Saphir and Amromin, 1948).

And, in any event, have we any right to call the standard operation a "radical" mastectomy. As we shave off the breast and pectorals from the chest wall, do we wilfully forget the internal mammary nodes, separated from our knife by only a few centimetres, and situated in turn on a short cut to the root of the neck and in the closest proximity to the parietal pleura? It is true that cancers are commonly in the lateral half of the breast and that local recurrence in the anterior mediastinum does not often confront us in clinical practice. But when we talk of the "radical" operation can we honestly overlook the work of Handley and Thackray (1949) for the implication of their findings is immensely significant and it has been abundantly confirmed in the recent contribution of Dahl-Iverson (1951).

If the limit of the resection in depth must be regarded as highly unsatisfactory, nothing better can be said of the upper and lateral limit of lymph node removal, somewhere in the inaccessible corner between the clavicle and the first rib—a significantly long way short, of the point, where the lymph drainage system eludes our further pursuit, by emptying into venous channels. For it was in this area that Andreassen (1947) found a 21 per cent recurrence rate after the radical operation, and when later (Dahl-Iverson and Andreassen, 1949) he undertook routine supraclavicular node dissection (when there was clinically no suspicion of their involvement) he found them to contain deposits of cancer cells in one out of every three cases with positive axillary nodes. Should we then extend the operation in all cases where there is already axillary node involvement to include a resection of the supraclavicular nodes? It was Halstead's practice (1907) to do a complete dissection from the clavicle to the carotid bifurcation whenever he encountered at operation metastases at the apex or even at mid-axillary level. Although this meant extending the operation in rather more than half his cases, it was completed with a low operative mortality. Unfortunately, the salvage rate was little encouragement to such enterprise. Haagensen and Stout (1943) have now relegated to the "categorically inoperable" all patients with clinical evidence of supraclavicular node involvement, yet they continue to sanction the "radical" operation.

when there is cancer in the axilla, although we are told that in one-third of these, the nodes above the clavicle are, at least microscopically, already involved. Does not all this add up to the frightening inadequacy of the "radical" operation, and little wonder that Lees and Park (1951) have attributed such improvement as follows surgery to no more than the wise selection of the patients in whom the disease seems likely to run a more benign course. Are we then to abandon surgery as our primary method of treatment, or will we be undismayed and accept the challenge as Wangensteen (1950) (in discussion, Taylor and Wallace, 1950) has done and pursue the disease beyond the clavicle and into the mediastinum, splitting the sternum to clear the lymphatics from around the great vessels and the internal mammary chain? I do not pretend to know the answer, and I would be reluctant to defend the practice of such wide resections, but of the depressing results at present achieved in breast cancer I am acutely aware as I am conscious of the limitations of the "radical" operation in even its local resection.

(10) *By an elaboration of new techniques which allow of resection of cancer at sites previously considered inoperable*

It is only within the last decade that attempts at surgical cure of cancer of the œsophagus have become at all frequent. When the risks of exploration across the pleural space has been removed, and the possibilities of restoration of continuity had been established, not by the tedious fashioning of an ante-thoracic œsophagus, but by anastomosis of the stomach even high up in the mediastinum, there was every hope that surgical endeavour might, at long last, hold out some promise of cure in this very lethal cancer. Unhappily there has been as yet little encouragement or reward in this field of surgery, where a low resectability rate, a high post-operative mortality and a small per cent of ultimate cures seem still to be the rule. Similarly, the enthusiasm which greeted Whipple's early efforts (1938) to resect malignant disease in the pancreas has now largely abated and the operation, at least for lesions in the head and body, likely to be practised with a declining frequency (Cattell and Warren, 1951, Loggan and Kleinsasser, 1951). The results of resection of ampullary tumours are, however, highly gratifying, always provided the diagnosis can be established at an early stage, and here at least a new technique has brought the occasional success.

The lead given in this country by Gordon-Taylor (1935) has been largely responsible for the increasing recourse to the hind-quarter amputation. He was able to record early this year (1952) no less than 50 cases from the practice of the Middlesex Hospital alone. For the cure of the massive secondary chondrosarcoma of the innominate bone or of the upper end of the femur, experience seems to justify it unquestionably, although in the management of the more lethal of the primary bone tumours the results are not so encouraging (Coley, Higinbotham and Romieu, 1951).

THE CASE FOR THE OTHER SIDE

I believe that all the many arguments which have been adduced at one time or another, in support of a widening of the surgical treatment of cancer, deserve our closest attention. At the same time, it is increasingly apparent that we must continuously and critically examine the implications and results of this trend in our surgical approach. For even in these types of cancer for which wider surgery is pled with most earnestness, a strong case can equally be made, if not for conservatism, certainly for the exercise of reasonable restraint. I have already touched on many of the points which may be argued in making the case for the other side, but perhaps I might now be allowed to marshall a few of them together.

(1) By extending our surgical excision, we may be inviting a prohibitive mortality. Are we right to sacrifice more, in the hope of curing more? Is it reasonable to deny a short span of life, maybe months, maybe years, to many in the hope of extending life usefully to a few? Are the extra lives we lose in the immediate post-operative period, made good by the prolonged survival of a small number or by the ultimate survival of a handful?

(2) All too often, extensive operative procedures are followed by a distressing morbidity. Are we going to add to the burden of the cancer sufferer the trials of a long and complicated post-operative period with no certain promise of cure in the end—the intractable fistula, the sloughing and slow healing of skin flaps, the large infected cavity and its painful healing.

Mixed up inextricably with this aspect of the problem is the difficult question of palliation, and bound up in it too is the surgeon's reluctance to define terms such as "operability" and "resectability". We can seldom forecast whether or not any operation is likely to be palliative. We can sometimes reasonably hope from our experience that it may be so, but it is only at death or thereabouts that we can make a just appraisal. When outlining treatment we must always try to bear in mind the likely behaviour of the tumour untreated, helped by what we know of its histology and of its observed growth to date. Of the merit of resecting a fungating rectal growth I am convinced, in the presence of hepatic and even of pulmonary metastases. We may not thereby prolong life (Modlin, Walker, 1949) but we do frequently and materially relieve distressing symptoms. It is unhappily true, however, that all too often an operation planned to be palliative turns out to be no more than meddlesome, and seldom does the reverse hold true. Before we embark on any attempt at palliative surgery we should first earnestly put to ourselves the question, "What are we endeavouring to palliate?" just as we should see to it later on that we give an honest answer to the further question, "How far have we succeeded?" Generally speaking, there can seldom be much justification for heroic palliative resections with a high risk of a complicated and tedious convalescence.

(3) Following our wide resection the functional disability or the

deformity may be intolerable even to one who is lucky enough to have been cured of his disease. Is it fair, for example, to rob a man of his tongue and jaw and to condemn him to a life of tube feeding? What of the crippling which follows a hind-quarter amputation? Is a wet colostomy compatible with a full life, or does it imply virtual social ostracism?

To each of these questions we must have a reasoned answer, given with sympathy and understanding, bearing closely in mind the influence of such happenings on our own patient. As Stammers (1949) so aptly put it "Life is quality, not quantity". Survival alone can never be enough, comfortable survival is the lowest standard by which we can be allowed to judge our success or failure.

(4) There is one danger against which we must constantly be on our guard when we consider the place for heroic resections. Increasingly every new problem will become a fresh challenge, which, be it from resolution or from pride, we feel bound to accept. This should be all to the good, but I suspect that in the process our judgment may fail, and we may commit the grave sin of failing to appreciate our limitations in the battle for cure. The cold verdict of the statistician helps much to curb such immoderate enthusiasm.

Now it is apparent that these arguments are largely dependent on purely personal considerations—on a knowledge, not, for example, of what total glossectomy can achieve in the treatment of lingual cancer, but of what it has to offer to our own patient, to Mr Smith or Mr Jones. For if in his management, there is any question of alternative methods of treatment, of a safe palliative procedure or of a hazardous attempt at wide resection for cure, the responsibility for the choice is only the surgeon's. If he knows his own mind, and surely he ought to, he can never reasonably transfer the burden of choosing to his patient's shoulders. And, in making the choice, he will do well to be influenced, no less by a fair and sympathetic appraisal of the patient who has surrendered himself into his care, than by the cold objective direction he receives from the pathologist, from follow-up results or from the cumulated experience of his colleagues. Only in this way will we be able to recognise the adventurous but wise from the enthusiastic but unreasoning, the understanding from the uncompromising, the hero from the butcher.

And finally, so long as the surgeon strives to improve the chance of cure in cancer, so he will tend continuously to widen his resection, and we would not have it otherwise. But the limitations of any attack on cancer which depends for its success only on development in this direction, must be obvious, increasing endeavour is likely to earn only a diminishing return. A consciousness of the limitations of surgical methods, however elaborate and however extended, will do us no good if it only damps our ardour and tempts us to give in, and valuable only if it leads to an intensification of efforts towards an understanding of the nature of malignant growth and of its complete control.

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POST-PARTUM BLOOD PRESSURE LEVELS

By HUGH R. ARTHUR, M.B., F.R.C.S.E., M.R.C.O.G.

Assistant Obstetrician and Gynaecologist

and

J. D. CHALMERS, M.B., CH.B., D.C.H., D.O.BST., R.C.O.G.

Lately Senior Obstetric House Surgeon

*From the Department of Obstetrics and Gynaecology, Newcastle
General Hospital*

THE occasional occurrence of unexpected hypertensive phenomena in the immediate post-partum period suggests that in some patients the stability of the blood pressure may be markedly affected by the process of labour.

The regular recording of the blood pressure during pregnancy is now an established practice. Blood pressure levels during labour have been investigated from time to time, and it is known that a transient rise occurs during the uterine contractions, most markedly in the second stage. There is, however, very little evidence to show the effect of labour as a whole on the blood pressure level, and no published record of it at the end of the third stage. Current textbooks make scant reference to it, and a fairly extensive search of the literature failed to reveal any paper on the subject apart, of course, from those in which the blood pressure level is used to check the patient's general condition in cases of shock or hæmorrhage.

This investigation was therefore planned in an attempt to find out, firstly, whether labour has any uniform effect on the blood pressure, and, secondly, whether there are any cases in which unexpected hypertension does occur. It has been the practice in this department to record the blood pressure within an hour of the completion of labour irrespective of the patient's previous clinical condition, and an analysis was undertaken of the delivery records between 30th June 1948 and 1st July 1950.

MATERIAL

In the two-year period 2863 patients were delivered, and of this number 862 cases had no record of the post-partum blood pressure readings. The loss of this number of records does not invalidate the statistical results of the analysis since the incomplete records are scattered evenly throughout the series and the effect of their loss is minimal. The general conclusions, therefore, drawn from the analysis of the remaining 2001 cases are valid.

Since so many factors influence the blood pressure it was difficult

to establish the maximum limit of normality, but after due consideration it was decided to accept 140/90 as the upper limit of normal, and any case showing a post-partum blood pressure reading higher than this was included

Of the 2001 cases analysed, 1758 (87·7 per cent) were found to have normal blood pressure readings after delivery was complete, and 243 (12·3 per cent) were found to have hypertension by the standard referred to above

Clearly a proportion at least of the 243 cases of post-partum hypertension would be cases of toxæmia or hypertension in which the raised blood pressure of the antenatal period was carried over into the puerperium. The group, therefore, was analysed for evidence of ante-partum hypertension and 126 cases were found (51·9 per cent). In addition 11 cases (4·5 per cent) were found to have incomplete antenatal records. The remaining 106 patients (43·6 per cent) were those in whom there was no hypertension during pregnancy or at the beginning of labour, and in whom the immediate post-partum hypertension was completely unexpected. This last group represents 5·3 per cent of the whole series of 2001 cases

ANALYSIS

Further investigation of these cases seemed desirable, and a study of the clinical histories showed that the degree of hypertension was not gross in the majority, the following table shows the distribution at various levels of blood pressure

140/90 - 150/100 mm Hg	81 cases
151/101-170/120 mm Hg	21 "
Above - 170/120 mm Hg	4 "

In the majority of the patients daily blood pressure recordings were not made in the puerperium, but in the 4 highest the charts show a steady fall during the first five days after delivery. Treatment was not recorded except in the highest group, and in these it followed the orthodox line of morphia followed by phenobarbitone, low salt diet and complete rest in bed

The progress of these cases, therefore, can only be judged by the blood pressure recordings on discharge from hospital and at the follow-up examination in the Post-natal Clinic eight weeks after delivery. On discharge from hospital the distribution of cases according to the height of the blood pressure, was thus —

Below - 140/90 mm Hg	58 cases
140/90 - 150/100 mm Hg	11 "
151/101-170/120 mm Hg	12 "
Above - 170/120 mm Hg	5 "

From this table it would appear that the degree of hypertension ten to fourteen days after delivery was rather more severe in many cases

than immediately after delivery, but account must be taken of the emotional instability of puerperal patients, particularly when faced with an examination by the doctor on which their discharge from hospital depended. This probably accounts for a large number of the hypertensive records at this examination, but the hypertension is transient and many of the patients undoubtedly belong to the large group of the population who have a labile blood pressure.

A true picture of the progress is gained by study of the blood pressure records at the Post-natal Clinic. Here it was found in the group under analysis, the cases were distributed thus —

Below 140/90 mm Hg	79 cases
140/90-150/100 mm Hg	Nil
151/101-170/120 mm Hg	1 case
Above 170/120 mm Hg	1 „
No record	25 cases
	(These represent cases who did not attend the Clinic)

It is thus apparent that in only a small percentage of patients is the unexpected immediate post-partum hypertension an indication of a truly hypertensive state, and in this small number a much longer follow-up would be needed to establish that hypertension was permanent.

An attempt has been made by further analysis of the whole series of 106 patients to find some common ætiological factor to account for the unexpected hypertension.

(1) *Age* — Age appears to throw some light on the problem. The distribution was recorded in age groups according to the following table —

	Puerperal hypertension	Antenatal hypertension
(1) Under 20 years	6	7
(2) 20 to 30 „	72	67
(3) 30 to 40 „	24	46
(4) Over 40 „	4	6

It is clear that by far the greater number fall into the twenty to thirty age group, and if this fact is assessed in conjunction with an analysis by the same age groups for the cases with established antenatal hypertension, it will be seen that the ratio is approximately the same in both series. In the former 1 12 4 1 and in the latter 1 9 6 1. Thus unexpected puerperal hypertension occurs most frequently in patients whose ages fall into those groups which show the highest incidence of toxæmia of pregnancy. This is suggestive of a toxæmic origin for rise in blood pressure after labour in patients apparently normal.

(2) *Parity* — If the suggestion made under consideration of the age groups is true then analysis for parity should show a preponderance of primiparæ. Of the 106 cases 57 were primiparæ and 49 multiparæ, the preponderance therefore is slight, but it does support the suggestion though not so strongly as might be expected.

(3) *Maturity* —For this analysis the cases were divided into three groups —

- (1) Those who came into labour within four weeks of the expected date
- (2) Those who were delivered at term
- (3) Those who were delivered up to two weeks after the expected date

In these three categories there were 35 premature, 50 full term and 21 who went into labour after the expected date. It appears, therefore, that the duration of the pregnancy also supports the suggestion that the unexpected hypertension may be a delayed toxæmic phenomenon, since premature onset of labour is a common finding in toxæmia of pregnancy, and a proportion of 35 premature to 50 full term deliveries in a series of 106 cases is much above the average.

It seemed reasonable also to assess the possible effect of labour upon the blood pressure, and in order to do this the series was analysed for length of labour, type of delivery, use of anæsthesia and third stage complications.

(1) *Length of Labour* —Ninety-one of the cases were found to have had a total duration of labour of less than twenty-four hours. It is therefore clear that prolongation of labour does not result in elevation of blood pressure, and indeed one would not expect it to do so, for such patients are in a state of physical exhaustion when the blood pressure tends to be low. Of the remaining cases 10 had labours up to forty-eight hours in duration, 5 over forty-eight hours and there was one elective Cæsarian section.

(2) *Type of Delivery* —Ninety-eight of the deliveries were normal, 4 were forceps deliveries, 3 were twin deliveries, and one was an elective Cæsarian section. Instrumental delivery therefore plays no part in this problem. This is borne out by the next factor.

(3) *Anæsthesia* —One hundred of the patients had no form of surgical anæsthesia, the remaining 6 having general anæsthetics. Analgesia was used in all cases of normal delivery, pethidine and chloral being the drugs in common use, and gas/air and trilene inhalations only at the end of the first stage and during the second stages.

(4) *Third Stage Complications* —Of the 106 patients under review only 9 are recorded as having a post-partum loss of blood between 10 and 20 ounces, and only in one case was the placenta removed manually, the reason being failure to separate, without hæmorrhage. This last patient developed hypertensive cardiac failure following the manual removal and died. Autopsy revealed a large suprarenal tumour.

It therefore seems clear that the type of labour and delivery have little, if any effect, on blood pressure even in the immediate post-partum period.

DISCUSSION

It appears from the investigation of these 2001 unselected patients that immediately after delivery the blood pressure remains within normal limits in the majority of cases. In the cases where it is found to be raised, approximately half show an antenatal hypertension which anticipates a post-partum reading above the normal, but in the remainder there is no previous abnormality of the pregnancy and the finding is unexpected.

In discussions on post-partum eclampsia the validity of the diagnosis has been questioned, and the view has been taken that when post-partum eclampsia occurs there has been an ante-partum toxæmia which has been missed. It now seems clear that such may not be the case and that hypertension may occur *de novo* immediately following labour. This is probably the explanation of the occasional case of unexpected hypertensive cardiac failure following labour. Since these two serious complications occur, even though infrequently, it seems reasonable to suggest that routine recording of the post-partum blood pressure should be made at the same time as the pulse and temperature.

The explanation of this sudden rise in blood pressure is not clear. The analysis of the cases in this series did not reveal any factor in the labours which would predispose to such a finding, but it is worth noting that prolonged or difficult labours which leave the patient exhausted were conspicuously absent, and that the finding was made almost entirely in young patients who had had normal labours. The most likely possibility is that the condition is a manifestation of sub-clinical toxæmia which is brought to light by the strain of labour in patients whose blood pressures are unusually labile. As has been shown, the majority of patients who show this rise in blood pressure have no other accompanying clinical symptoms or signs, and their progress with usual methods of treatments is good. The frequency, however, with which the condition occurs (1/20 cases) and the possibility of the more serious conditions of post-partum eclampsia and hypertensive cardiac failure arising seems to justify a more careful watch on the blood pressure immediately following delivery than is at present usual. A further analysis is required to confirm or modify the findings of this paper, and this is being undertaken.

SUMMARY

(1) Two thousand and one records of delivery were examined for blood pressure recordings immediately after labour. One thousand seven hundred and fifty-eight were found to be within normal limits and 243 (12.3 per cent) to be raised.

(2) Of the 243 cases in the hypertensive group 126 were found to have evidence of ante-partum hypertension, 111 had incomplete records and 106 (43.6 per cent) had no evidence of any rise in blood pressure either in pregnancy or at the beginning of labour.

(3) The 106 cases (5.3 per cent of the whole series) of unexpected post-partum hypertension were analysed for the type of labour and for the general factors of age, parity and maturity. No common ætiological factors were found.

(4) Follow-up of the cases showed that in the majority (at least 75 per cent) the hypertension had disappeared in two months without special treatment.

(5) A suggestion is made that this may be a manifestation of sub-clinical toxæmia.

(6) In view of the occasional occurrence of post-partum eclampsia and hypertensive cardiac failure, it is suggested that the result of the investigation justifies and necessitates routine recording of the blood pressure at the end of labour.

We are indebted to Mr Linton Snaith for permission to use the case records quoted in this paper.

OBSERVATIONS ON THE PLASMA FIBRINOGEN CONTENT AFTER MYOCARDIAL INFARCTION

By ELIZABETH GILCHRIST, M A, B Sc, Ph D

Department of Clinical Chemistry

and

JOHN A TULLOCH, M C, M D, M R C P E

Department of Cardiology

Royal Infirmary, Edinburgh

FIBRINOGEN is one of the proteins normally present in plasma, and is constantly utilised within the body. In the healthy adult approximately 6 g are synthesised by the liver and are metabolised each day (Everett, 1946). Much larger quantities are formed in the presence of inflammation, which with injury is the most powerful stimulus to fibrinogen production. The stimulus does not depend on bacterial products, as sterile or aseptic inflammatory processes have the same effect. Meyers (1948) has shown that myocardial infarction is followed by a rise in plasma fibrinogen. He suggests that determination of the fibrinogen levels in the plasma may be a valuable guide to the progress of the reparative process in the infarcted area. The present investigation was undertaken to determine (a) the frequency with which increase in the plasma fibrinogen content occurs after a coronary thrombosis, and (b) the relation, if any, of the clinical severity of the case with the degree and duration of the changes observed.

MATERIAL

Forty-two patients were studied during forty-five attacks of coronary thrombosis—33 males, 3 of whom have been observed during two attacks, and 9 females. All were inpatients in the Royal Infirmary, Edinburgh, and all showed electrocardiographic evidence of recent myocardial infarction. Serial estimations of plasma fibrinogen content were carried out at frequent intervals during the period of hospitalisation. Seven patients were treated conservatively, while anti-coagulants were employed in the remaining 38 patients. Seven deaths occurred during the period of observation, 2 of these patients were treated conservatively, and 5 received anti-coagulants. In addition, plasma fibrinogen estimations were carried out on 10 healthy male adults as controls, and to establish the normal for the method used.

METHOD

Blood samples were collected at 9 a.m. each day, except on the day of admission. A clean venepuncture was performed, blood was withdrawn into a dry sterile all-glass syringe and was immediately transferred to a specially prepared glass tube graduated at 6 ml and contain-

ing the optimum amount of oxalate—30 mg to 6 ml of blood * Thorough mixing of the oxalate powder with the blood was ensured by corking the tubes and inverting gently several times Hæmolysis was avoided

Fibrinogen was estimated by the following method To 2 ml of plasma there were added 30 ml of 0.9 per cent sodium chloride and 1 ml of 2.5 per cent calcium chloride, and the mixture was incubated overnight at 37° C The clot which had formed was collected on a fine glass rod and dried on a filter paper, care being taken that none was lost The nitrogen content was estimated by the micro-kjeldahl method, and the fibrinogen content calculated using the factor 6.25 The accepted figures for the normal range of plasma fibrinogen is

TABLE I

This Illustrates the Distribution of the Maximum Plasma Fibrinogen Levels Observed in 32 Patients with a Recent Coronary Thrombosis, and their Relation ship to the Severity of the Attack as Divided Clinically into Three Grades, Mild, Moderate and Severe

Maximum Plasma Fibrinogen	Number of Cases of Coronary Thrombosis			
	Total	Clinical Assessment		
		Mild	Moderate	Severe
0.30-0.39 g per cent	1	1		
0.40-0.49 "	3	2		1
0.50-0.59 "	10	9	1	
0.60-0.69 "	9	5	2	2
0.70-0.79 "	6	1	3	2
0.80-0.89 "	1		1	
0.90-0.99 "	2		1	1
Total	32	18	8	6

between 0.2 and 0.4 g per cent In the 10 control cases investigated the results obtained by the method above varied from 0.24 to 0.32 g per cent

DISCUSSION

The time after the acute attack at which the patients first came under observation varied widely thus 3 cases were already in hospital at the time of their coronary occlusion, while, at the other extreme, one patient was not admitted until twenty-two days after the infarct had been sustained The cases studied fall into two groups (a) 32 patients investigated from within one to five days after the onset, and (b) 13 patients admitted between the eighth and twenty-second day after the infarct In 30 of the 32 cases in group (a) the plasma showed a rise in fibrinogen content to abnormally high levels during the first or second weeks after the myocardial infarction, the highest recorded level being 0.98 g per cent From Table I it will be seen that in the majority of cases the

* These tubes were prepared by adding 0.5 ml of 6 per cent sodium oxalate to each tube and drying them in an oven at 100° C till the oxalate remained as a powder

maximum figure lay between 0.50 and 0.79 g per cent. In the remaining 2 cases of this group the highest levels were at the upper limit of normal, viz., 0.39 and 0.40 g per cent respectively. Since in these patients the first estimations of fibrinogen were lower, a minor rise did occur. Six patients were examined on the day of the attack, 11 on the second day and 15 between the third and fifth day after the infarct occurred. Of the 6 patients seen on the first day, 3 were examined within three to six hours after the onset and at that time showed normal fibrinogen levels. The other 3 patients were not examined till ten to seventeen hours had elapsed and these all showed abnormally high levels. Of the 11 patients seen for the first time on the second day, all had plasma fibrinogen levels above the normal range, while of the remaining 15 patients examined for the first time between the third and fifth day after the acute incident, only 3 gave first readings still within the normal range, viz., 0.36 and 0.38 and 0.39 g per cent.

TABLE II

The Day on which the Maximum Plasma Fibrinogen Level was Recorded in 32 Cases of Coronary Thrombosis, is Shown

Day After Onset	Number of Cases	Day after Onset	Number of Cases
2nd	2	9th	1
3rd	3	10th	0
4th	3	11th	2
5th	7	12th	2
6th	5	13th	0
7th	4	14th	2
8th	1	15th	0

respectively. These figures are near the upper limit of the normal range and may have been high for the patients in question, so that the rise though slight may have started.

The times at which the highest levels occurred and the subsequent fall started varied considerably in different patients. Reference to Table II will show that the common peak period lay between the fifth and the seventh day after the attack. In a few cases the highest level was attained more slowly and occurred between the tenth and the fourteenth day of the illness. As the samples of blood for estimations were not withdrawn every day but with a few days' interval between, it is possible that in some cases the highest level of plasma fibrinogen reached may have been missed. This must be borne in mind when considering the results. It would appear, however, that in general there is a rapid rise in plasma fibrinogen to a maximum during the first week after the infarct occurs.

In all the cases studied this steep rise in the early stages of the disease was succeeded by a gradual return of the plasma fibrinogen levels to within normal limits during the succeeding weeks. This is

illustrated in Fig 1. The fall occurs over a varying period of time. Excluding the 2 patients who showed only a slight rise within the limits of normal and 5 patients who died during the first few weeks, 25 cases remain for analysis. Nine of these showed a return of the plasma fibrinogen to within the normal range during their stay in hospital, *i.e.* within six weeks after the attack. The duration of the abnormal levels in these patients ranged from fifteen to thirty-six days after the occurrence of the coronary thrombosis. The maximum level attained

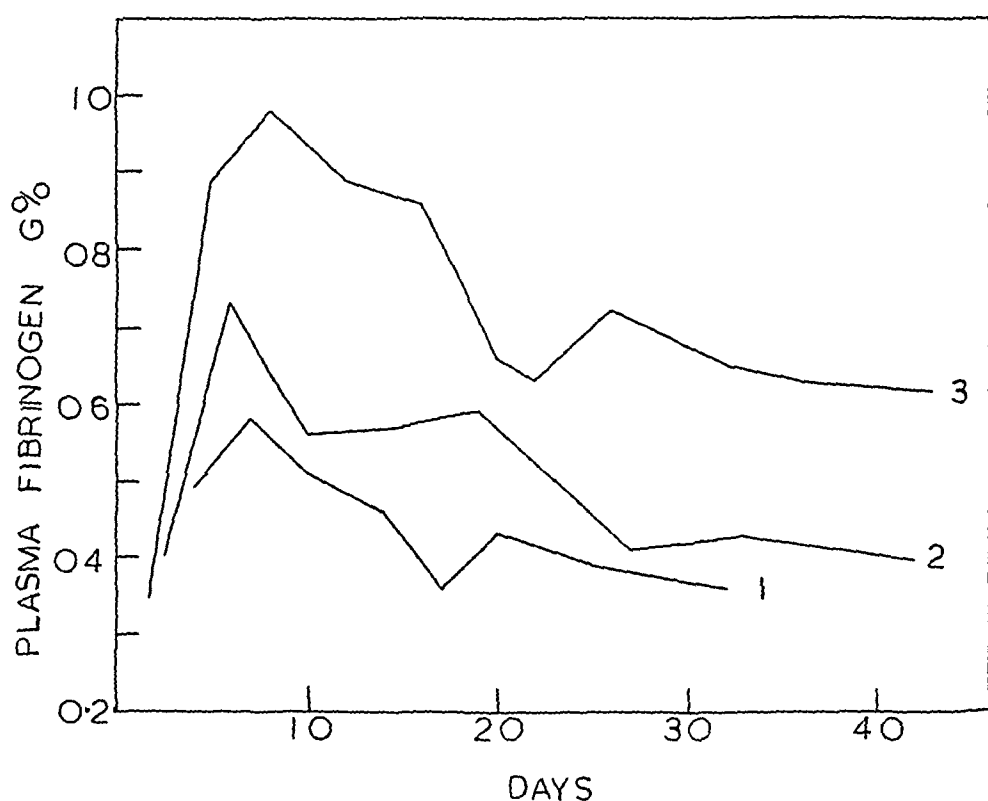


FIG 1—The changes in plasma fibrinogen content observed in 3 cases of coronary thrombosis are illustrated. The extreme variation in the magnitude of the increase in plasma fibrinogen and its duration are well known. Clinically Case 1 had a very mild attack, Case 2 was moderately severe, while Case 3 was seriously ill.

was under 0.6 g per cent in 6 of the 9 cases, and was lower than that reached in the other 16 cases of the group under consideration. These 16 cases had not only a higher maximum level—only 3 showed a figure under 0.6 g per cent—but the return to normal was much slower. The final reading prior to discharge from hospital was still above the normal level. Nine of these 16 cases have been followed up six weeks after their discharge from hospital, *i.e.* they were under observation for three months after the coronary thrombosis had occurred. Five had returned to normal plasma fibrinogen levels at that time, and 4 were still above normal, *viz.* 0.41, 0.43, 0.44 and 0.49 g per cent respectively. As already stated 5 of the patients died, 4 in congestive

heart failure and I suddenly and unexpectedly. In these cases the serial levels of fibrinogen did not differ materially from those obtained in the patients who survived.

Comparison of the rise in plasma fibrinogen levels with the severity of the coronary thrombosis—the latter being assessed on clinical grounds in all cases by the same physician—shows that the more severe attacks tend to be associated with the higher levels of fibrinogen in the plasma (Table I). Determination of blood sedimentation rate was done throughout the course of the illness in all the patients, and it was found that in most cases the B S R changed in a fashion roughly

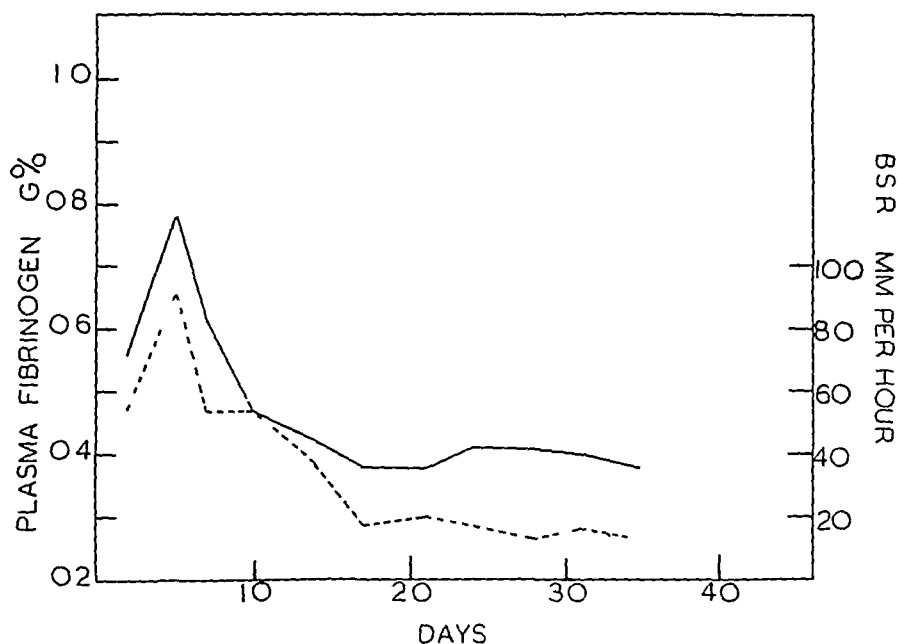


FIG. 2.—Serial observations made on the plasma fibrinogen content (continuous line) and on the blood sedimentation rate (dotted line) in one moderately severe case of coronary thrombosis are illustrated.

parallel with the rise and subsequent fall in fibrinogen. The closeness of the correlation has not, however, been mathematically examined. Fig. 2 illustrates this point, the curves shown by these two factors tend to be parallel to each other, although the fall in plasma fibrinogen may lag behind that of the B S R. Comparison of individual cases shows that a particular plasma fibrinogen level is not associated with a particular B S R reading and *vice versa*, thus a B S R of over 100 mm/hr has been observed with plasma fibrinogen levels of 0.63 and 0.43 g per cent, while B S R's of approximately 50 mm/hr occurring two weeks after the infarct have been associated with plasma fibrinogen levels ranging from 0.41 to 0.78 g per cent.

The 13 patients in group (b) were first investigated between the

eighth and twenty-second day after the coronary thrombosis was sustained. These have been analysed separately. One patient died on the twelfth day, while 12 survived. All received tromexan. All but one showed abnormally high plasma fibrinogen levels from the beginning of examination. Eleven patients admitted between the eighth and nineteenth days showed a rise in plasma fibrinogen level during the first few days of their investigation, the increase observed varying from 0.03 to 0.27 g per cent. The maximum level was observed on the twelfth and thirteenth days after the infarct in 3 patients, on the seventeenth day in 2, and between the twentieth and twenty-fourth days in 6 cases. Thereafter the fibrinogen levels fell gradually towards normality. Two cases admitted on the thirteenth and twenty-second days respectively showed no such initial rise in fibrinogen content during the first few days after admission. As in group (a) one-third (4 of the patients) showed plasma fibrinogen levels within the normal range in twenty-four to thirty-six days after the infarct, while two-thirds (8 patients) still showed fibrinogen levels greater than 0.40 g per cent at the time of their discharge from hospital. Three of these latter 8 patients have been examined six weeks after their discharge, and in 2 the fibrinogen levels were still high, being 0.40 and 0.41 g per cent respectively.

The fibrinogen estimations recorded in the patients in group (b) differ in one important respect from these obtained in the group (a) patients. The rise in plasma fibrinogen content in the 11 patients described above occurred at a time when, in the group (a) patients, the fibrinogen levels had begun to fall. Some factor other than the myocardial infarct, and common to all cases would therefore appear to be involved. Tromexan administration may be this factor, as all cases were so treated. Dicoumarol is known to influence fibrinogen production by the liver (Irish and Jaques, 1945), temporarily stimulating fibrinogen production when administered in moderate dosage, and damping down fibrinogen production when given in massive dosage. It is therefore possible that tromexan administration in therapeutic dosage may temporarily stimulate fibrinogen production by the liver. This is at present under investigation. In the group (a) patients who received tromexan (24 cases) or dicoumarol (1 case) this effect of the coumarol drug may be overshadowed by the more powerful stimulus of the myocardial infarct. The 7 patients in group (a) who were treated conservatively differed in no respect from those receiving anti-coagulants, except in so far as the maximum level recorded did not exceed 0.79 g per cent. The numbers involved are too small to draw definite conclusions.

SUMMARY

An increase in plasma fibrinogen content occurs after myocardial infarction. The maximum increase is detected about one week after the acute episode, and is succeeded by a gradual fall in plasma fibrinogen

levels. In one-third of all cases, the level has returned to within normal limits by the sixth week after the onset, but in the remaining two-thirds, the readings are still abnormal at this time. Plasma fibrinogen estimation may therefore be an additional aid in establishing in retrospect the diagnosis of coronary thrombosis. In some cases the levels may still be abnormally raised three months after the acute incident. The more severe cases tend to show the greatest rise in plasma fibrinogen, and in these a longer time elapses before a normal level is restored. Patients observed from the onset react similarly whether treated conservatively or with anti-coagulants. Patients first treated with anti-coagulant therapy from the eighth day after the attack, or later, show a further rise in plasma fibrinogen content from an already abnormally high level. This may be related to tromexan administration.

All patients were under the care of Dr A. Rae Gilchrist. We are indebted to him for permission to carry out the investigation, and also to Dr C. P. Stewart for the laboratory facilities provided.

REFERENCES

- EVERETT, M. R. (1946), *Medical Biochemistry*. Second Edition, pp. 70, 414.
 MEYERS, L. (1948), *Arch. Int. Med.*, **82**, 419.
 IRISH, U. D., and JACQUES, L. P. (1945), *Amer. Journ. Physiol.*, **143**, 101.

NEW BOOKS

Statistics for Medical and other Biological Students By L. BERNSTEIN, B SC, M R C S, L R C P, and M. WEATHERALL, M A, D M, B SC Pp xii+180, with 17 figures Edinburgh E & S Livingstone 1952 Price 18s net

The practical usefulness of a knowledge of mathematics in medicine, and particularly in medical research, has long received inadequate recognition, and this is an attempt to correct the fault. The authors are scientists, lecturers in physiology and pharmacology, and they have a sound knowledge of the needs of the medical man. Descriptions of the various essential methods are full, simple and understandable. Typical problems are given and worked out in detail so that the various steps can be readily followed. Tables of squares, square roots, logarithms and other useful aids are included, so that the book can be used as a guide to the solution of practical problems. This is an attractive little volume and should become popular.

An Atlas of General Affections of the Skeleton By SIR THOMAS FAIRBANK, D S O, O B E, M S, ETC Pp xx+411, with 510 illustrations Edinburgh E & S Livingstone Ltd Price 55s net

The interest and great experience of Sir Thomas Fairbank in skeletal conditions is so well known that the advent of this textbook has been eagerly awaited.

In the introduction there is given a classification of the various affections according to their etiology, so far as this is known, and this order has been followed throughout the book. This etiological classification is—congenital developmental errors, acquired affections of unknown origin, those due to diet and metabolism, endocrine errors, infections, errors of the hæmopoietic and lymphatic systems, and multiple neoplasms. There are still many cases which cannot be placed in a recognised group, but so far as this complex subject can be classified the author does it, and nobody could do it better. There are some very helpful tables on such differential diagnostic features as blood chemistry, dwarfism, increased density of bone, and vertebral collapse. It is obvious, therefore, how very helpful such a book is to the clinician.

Most of the conditions, and particularly the rarer ones, are illustrated by individual cases given in detail. The descriptions of the affections of the reticulo endothelial system are very complete and helpful, and the author points out the intimate relationship of this group of conditions on account of the fundamental pathology common to all. There is no attempt to suggest treatment in any part of the book, as one would expect since so often there is none.

The book is copiously illustrated and the pictures and the X-rays are extraordinarily well produced. It is a classic and will be much cherished by those who own it.

Text Book of Ophthalmology Vol V By SIR STEWART DUKE-ELDER, K C V O Pp xxxii+5713 with 1181 illustrations including 32 in colour London Henry Kimpton 1952 Price 90s net

Each succeeding volume of Sir Stewart Duke-Elder's *Text Book of Ophthalmology* is eagerly welcomed by ophthalmologists all over the world and added to its predecessors to make an up to-date and exhaustive work of reference for clinical ophthalmologists and research workers alike.

Vol V deals with the ocular adnexa, the lids, the tear passages and the orbit, affections of which can be the most perplexing in the whole field of ophthalmology.

In many conditions of the eyelids the eye specialist has common ground with the dermatologist, and the numerous excellent pictures of such conditions are bound to prove a great help on many occasions.

In the section on the tear sac one cannot altogether agree that the operation of dacryocystorhinostomy requires "a surgeon who is an adept at a somewhat tricky technique." It would be a pity if this did anything to discourage the wider use of this most successful operation.

It is a pleasure to read Sir Stewart's easy, lucid writing, and the occasional historical reference or picture makes this volume much more than a solely scientific one.

Hippocrates on Intercourse and Pregnancy Translated by T U H ELLINGER, SC D, M A Pp 128 New York Henry Schuman 1952 Price \$2 50

The translator points out that most scholars agree that the author of these papers is not the great Hippocrates of Cos but some physician of the rival Cnidian school and that he wrote in the 5th century B C They appear in English for the first time Of the two papers, that "on the development of the child" is by far the more important and interesting, and it is surprising to learn how much was already known of the subject at that time

The author acknowledges help with the manuscript from a professor of Greek and a professor of the History of Medicine, and an introduction and a series of notes has been supplied by Dr A F Guttmader, professor of Obstetrics

This little book should be of interest to all medical men and particularly to those engaged in the practice of obstetrics

Cardiac Emergencies and Heart Failure By ARTHUR M MASTER, MARVIN MOSER and HARRY L JAFFE Pp 159, with 13 illustrations London Henry Kimpton 1952 Price 22s net

The authors hope this volume will be of value to general practitioners in dealing with the "acute heart" Much recommended therapy is outwith the facilities of general practice in this country Insufficient emphasis is given to dangers of new potent drugs recommended Thoroughly up to date, always stimulating and often provocative

Ciba Foundation Colloquia on Endocrinology Vol 1 Edited by G E W WOLSTENHOLME, OBE, MB, BCH Pp xx+315, with 13 pages of illustrations London J & A Churchill, Ltd 1952 Price 30s net

This is the first volume reporting the proceedings of colloquia arranged by the Ciba Foundation It has two parts, the first dealing with steroid hormones and tumour growth, and the second with steroid hormones and enzymes The parts are divided into sections, each containing a paper with references and the discussion which followed the paper Those invited to attend are distinguished workers from many countries and, as might be expected, the standards are high The Ciba Foundation is to be congratulated on its decision to allow a wider circle an indirect share in these valuable symposia

Rheumatic Diseases Based on the Proceedings of the Seventh International Congress on Rheumatic Diseases Edited by CHARLES H GLOUMB, MD Pp xxiv+449, with 126 illustrations London W B Saunders 1952 Price 60s

This volume has been prepared from papers or abstracts of papers presented at the Seventh International Congress on Rheumatic Diseases held in New York in 1950 The book is arranged so that papers dealing with various aspects of one subject or disease are grouped together Both the clinician and the research worker will find much to interest them The effect of cortisone and of A C T H on rheumatoid arthritis and acute rheumatic fever were first reported in detail at this conference by Hench and his colleagues, an event of historic importance in the field of clinical research It is a pity that there should be a delay of two years in publishing these papers, as much of the work reported has been published elsewhere in the interval

Called to Serve By PAUL GLIDDON and MURIEL POWELL Pp 127 London Hodder and Stoughton 1952 Price 7s 6d net

The doctor, the nurse and the chaplain each has a part in tending the sick, and this book describes the common foundation on which these professions are built, emphasises their vocation and shows how each is complementary to the other A helpful and stimulating book well worth reading by all who are Called to Serve

Surgical Forum—American College of Surgeons By Committee of Surgical Forum
Pp viii+667, with 290 illustrations London W B Saunders, Ltd 1952
Price 50s net

This volume presents the proceedings of the Surgical Forum of the Clinical Congress of the American College of Surgeons, 1951. More than 100 short papers are published in full and others are abstracted, these cover a wide field of surgery and experimental work related to surgery, and fully justify the claim made by Dr Owen Wangenstein in his Foreword that "the progress of surgery in America from year to year will be documented and reflected in these volumes". Most of the well-known surgical centres in America are represented by reports of research works and all the contributions are brief and readable. British surgeons will find here an acceptable answer to the question, "What's new in America?"

Elementary Medical Statistics By DONALD MAINLAND, M B, CH B, D SC, F R S E, F R S C Pp 327 Philadelphia and London W B Saunders Company 1952 Price 25s

This excellent book is highly recommended to all medical workers and students as simple to follow, interesting and instructive. It has a special appeal to the medical practitioner, though it covers all the basic practices of statistics. The author addresses himself to an audience interested in interpreting and evaluating medical experience—an audience whose needs he thoroughly understands and fully satisfies. He shows the theoretical aspects involved in forming judgments and works out all the practical steps required in every kind of investigation or experiment. The planning of the collection of data and the obtaining of a suitable sample are as fully explained as are the methods of analysis. Each chapter is full of examples and illustrations of many different types of investigation to guide every kind of reader. The common fallacies which lie behind "controlled" experiments, "impressions" from small samples, and clinical comparisons are also carefully studied.

The good points of this book are manifold. Introducing each chapter are valuable suggestions for the order of reading and possibly omission. The important and fully explained distinction between enumeration data and mensuration data will be of the greatest help to practitioners. The attention given to discussion of small difficulties and concepts too often glossed over is outstanding.

The book is written simply, documented fully, explained clearly and carefully and designed to hold the interest both of the novice and of the more experienced. The principles so ably expounded in the text will help practitioners in their work and in forming judgments of it. The author has indeed fulfilled his objectives of presenting statistics as a fundamental science and of proving the value of statistical thinking in clinical medicine.

Diseases of the Ear, Nose and Throat By G PORTMAN, M D Pp viii+728, with 666 figures London Baillière Tindall & Cox 1951 Price £7, 10s net

George Portman is well known for the post-graduate course in Otorhinolaryngology he conducted before the War. This book is based on the lectures and instructions he gave and is unique in the speciality. Prime place is rightly given to the clinical examination of the patient, special diagnostic procedures are kept in their correct perspective. In this country many of the tests described under the examination of the auricular apparatus would be considered out of date and redundant, the omission of the Hallpike differential cold caloric test is an example. The section on endoscopy reflects the continental school of thought predominantly, and the diverse methods described may be a little confusing to the student. The sections dealing with anatomy and radiography and the interpretation of X ray films call for special praise.

The publishers have to be congratulated upon the excellence of the illustration and plates, the translators, however, could have extended, with benefit, their activities to some of the explanatory data of the drawings. This book can be confidently recommended to all students of the speciality who wish to acquire a sound clinical and diagnostic technique.

NEW EDITIONS

Diseases of the Nervous System By F M R WALSHE Seventh Edition
Pp vi+365, with 63 illustrations Edinburgh E & S Livingstone 1952
Price 24s net

This magnificent book is unique in expressing both the distinguished author's personality and the common nervous disorders in a manner comprehensible to practitioners and senior students, for whom it is intended

One welcomes the way in which it stresses the importance of adequate history taking and clinical observation in this rather laboratory-minded era

Several sections contain new material and represent an admirably balanced interpretation of the most recent advances in the subjects considered This has not, however, diminished the original freshness of approach

The illustrations are excellent, the index thoughtfully compiled and the general production of a high standard

Recent Advances in Medicine By G E BEAUMONT, MA, DM, FRCP, DPH, and E C DODDS, DSC, PhD, MD, FRCP, FRIC, FRS (EDIN), FRS
Thirteenth Edition Pp iv+397, with 59 illustrations London J & A Churchill 1952 Price 27s 6d net

The thirteenth edition of this book contains new chapters on the collagen diseases, anti histamines and radio active isotopes Like the previous editions this book provides the postgraduate student with a concise yet detailed account of the main advances which are for ever taking place in medicine It is well written and is a most informative and useful little book

Massage and Remedial Exercises By NOEL M TIDY, MCSP, TMMG Pp viii+519, with 192 illustrations Bristol John Wright 1952 Price 27s 6d net

This book has now reached its ninth edition—a fact that proves its continued popularity with physiotherapy students

The present edition includes additional material on the arrangement of Group Exercises both for the young and aged, also sections on treatment of varicose and other ulcers by the Bisgaard method and on treatment of spastic paraplegias on the lines of Dr Guttmann's work at Stoke Mandeville It is a very complete textbook

Miss Tidy, while she attempts to move with the times and add some of the more recent advances in the physiotherapeutic procedures, would have been well advised to have omitted some of the more out moded forms of treatment The book would have been improved with considerable cutting

Textbook of Medicine By various authors Tenth Edition, edited by Sir JOHN CONYBEARE, KBE MC, DM, FRCP, and W N MANN, MD, FRCP
Pp vii+912 with 31 illustrations and 31 X ray plates Edinburgh E and S Livingstone Ltd 1952 Price 37s 6d net

For the tenth edition of this already well known textbook, Sir John Conybeare has secured the assistance of Dr W N Mann of Guy's Hospital as co editor Their purpose is to provide within as small a compass as possible the essentials of medicine for students and practitioners Difficult as it may be to achieve this purpose in the midst of constant changes and new developments, the editors have produced a textbook for which only the highest praise is applicable It has the merit, rare among current British textbooks of being completely up to date Numerous sections, particularly those dealing with treatment, have been re written The continued success of "Conybeare" is assured

A Textbook of Clinical Pathology Edited by SEWARD E MILLER, M D Fourth Edition Pp xxvi+1060, with 208 illustrations London Bailliere, Tindall & Cox 1952 Price 68s 6d net

The fourth edition of this book has been completely rewritten. Emphasis is given to the explanation of basic scientific facts and to the interpretation and evaluation of laboratory diagnostic methods. Detailed descriptions of highly skilled technical analysis are omitted from this book which deals solely with the practical procedures that can be performed in the side-room of any ward. The book is designed to give the medical student, postgraduate and teacher of clinical medicine an authentic source of basic scientific information and how to interpret this knowledge in the presence of disease.

Atlas of Human Anatomy By F FROLINE, M BRODEL and L SCHLOSSBERG with a text by J F WILLIAMS New Edition Pp 88 with numerous illustrations in colour London Geo Allen & Unwin 1952 Price 16s net

This small and well-produced book is illustrated by drawings originally made for wall-charts and the figures though small are very full of detail. The new edition has been supplemented by ten new charts of the endocrine system in colours and by a large number of scale drawings of microscopic appearances.

The text is rather elementary in character and not detailed enough for the use of medical students but would be very suitable for the instruction of nurses, first-aid workers and the like.

BOOKS RECEIVED

- AINSWORTH, G C, B SC, PH D, F L S *Medical Mycology* (Sir Isaac Pitman & Sons Ltd) 15s
- BARTON WRIGHT, E C, D SC, F R I C *The Microbiological Assay of the Vitamin B Complex and Amino Acids* (Sir Isaac Pitman & Sons Ltd) 18s
- BETT, Dr W R *The Infirmities of Genius* (Christopher Johnson Publishers Ltd, London) 18s net
- COPE, V ZACHARY, M S, F R C S *Human Actinomycosis* (Wm Heinemann, Medical Books Ltd, London) 12s 6d net
- DAVIDSON, L S P, B A (CANTAB), M D, F R C P (LOND), M D (OSLO) *The Principles and Practice of Medicine* (E & S Livingstone Ltd, Edinburgh) 32s 6d
- GHOSH, Dr B N, F R C P S (GLAS), F R S (EDIN) *Pharmacology Materia Medica and Therapeutics* (Hilton & Co, Calcutta H K Lewis & Co, London) 30s net Rs 20
- LEDLIE, R C B, and HARMER, M *Aids to Surgery* (Bailliere, Tindall & Cox, London) 7s 6d net
- LEPINE, PIERRE *French English, English French Dictionary of Medical and Biological Terms* (H K Lewis & Co, London) 63s net
- MACKENNA, R M B, M A, M D, F R C P *Diseases of the Skin* (Bailliere, Tindall & Cox, London) 42s
- MASTER, GARFIELD AND WALTERS *Normal Blood Pressure and Hypertension* (Henry Kimpton, London) 30s net
- NICOLL, J T BELL *The Span of Time* (Hodder & Stoughton Ltd, London) 12s 6d
- TREDGOLD, A F, M D, F R C P, F R S (ED) *A Text book of Mental Deficiency (Amentia)* Eighth Edition (Bailliere, Tindall & Cox, London) 37s 6d net
- WALKER, B S, BOYD, W C, and ASIMOV, I *Biochemistry and Human Metabolism* (Bailliere, Tindall & Cox, London) 68s 6d net
- WILLIAMS, HARIFY *The Conquest of Fear* (Jonathan Cape, London) 16s net
- Edited by WORSTER DROUGHT, C, M A, M D, F R C P, F C S T *Residential Speech Therapy* (Wm Heinemann, Medical Books Ltd, London) 15s net
- YOUNG, W B *Basic Medical Physiology* (Interscience Publishers Ltd London) 58s

Edinburgh Medical Journal

December 1952

THE CHEMOTHERAPY OF URINARY TUBERCULOSIS

By WM G WIMSETT, L R C P, L R C S I

Robroyston Hospital, Glasgow

AT Robroyston Hospital, in December 1948, a controlled trial was instituted of streptomycin therapy for tuberculous disease of the urinary tract. This investigation, conducted under the auspices of the Tuberculosis Research Unit of the Medical Research Council, was concluded in December 1951. At the completion of the trial 137 patients had been studied. Selection of the cases for streptomycin treatment was made from a statistically prepared list kept at the M R C offices. Streptomycin has been given to 70 patients and 67 were selected as control cases.

The patients were grouped into five categories —

Group 1—Unilateral renal tuberculosis Minor lesion without cystitis

Group 2—Unilateral renal tuberculosis Major lesion necessitating nephrectomy, cystitis

Group 3—Bilateral renal tuberculosis Nephrectomy for the more advanced lesion

Group 4—Tuberculosis occurring in the remaining kidney subsequent to nephrectomy for unilateral disease

Group 5—(a) Major bilateral tuberculous lesions,
(b) Minor bilateral tuberculous lesions

Complete urological investigation was carried out on all patients whether treated by streptomycin or not. The investigation was repeated after treatment and thereafter the patients were observed and reassessed at intervals of three months. Tests for streptomycin resistance and assays of streptomycin levels were performed routinely. Observation on toxic effects with particular reference to vestibular damage were also made.

The patients treated by streptomycin were given one gramme daily in two 0.5 gm intramuscular injections for ninety days. Controls and streptomycin treated patients received similar general medical treatment.

Read at a Meeting of the Tuberculosis Society of Scotland held at Bangour Hospital, on 25th January 1952

In March 1950 a preliminary report was presented by Jacobs and Borthwick to the section of Urology of the Royal Society of Medicine. This report was based on the study of 90 patients. Streptomycin had been given to 46 and 44 had been used as controls. At the completion of the trial a further 47 patients had been studied. Analysis of the additional cases confirms the conclusions reached in the preliminary report.

Broadly these conclusions were —The treatment has no effect on an established caseocavernous lesion. By some process encouraging constriction there is a possibility that the focus, though itself remaining active, may become shut off. A regression of the constriction, however, can occur. Streptomycin therefore cannot be recommended to supplant surgery, and in clinical unilateral renal tuberculosis the diseased kidney should be removed, or, where possible, partial nephrectomy should be attempted.

Its automatic employment in cases unsuitable for surgery is not advised. Thus, when there is an advanced bilateral renal lesion or an advanced lesion in a solitary kidney, no improvement in the kidney lesion can be anticipated, and vesical contracture may be accelerated where cystitis was previously present.

In Group 2 cases, that is cases for nephrectomy, cystitis, streptomycin may prove beneficial as an additional measure possibly before as well as after surgery. In addition, it should afford some measure of protection against activation and development of the disease in the apparently healthy kidney. This statement is given with reservation, however, for at the completion of the trial, in Group 1 cases, the contralateral kidney became tubercle positive in 3 out of 10 treated cases, whilst this occurred in only 3 out of 11 controls.

Streptomycin does have a beneficial effect on secondary tuberculous cystitis, but this would appear to be relative to the presence and degree of disease in the upper urinary tract. Thus in Group 2 cases, that is those with a unilateral renal lesion in whom the affected kidney has been removed, cystitis has cleared and the urine has become tubercle negative in an appreciably larger number of streptomycin treated cases than has occurred with controls. In Group 5 cases, however, consisting chiefly of patients with well-established bilateral disease, no beneficial effect on the bladder resulted. In the few cases in whom the bilateral lesions were minimal, the effect of streptomycin on the bladder has been good.

Toxicity —As previously stated, particular attention has been directed towards the occurrence of vestibular damage. For each case, whether receiving streptomycin treatment or control, routine vestibular function tests were performed before and at the completion of treatment. The examinations were carried out under the direction of Dr John McKinlay, ear, nose and throat consultant to the hospital. Complete details of the results obtained are not yet available, but the following observations can be made.

The incidence of vestibular damage in streptomycin treated cases was high. In a number of patients the damage was slight, having been detected only after routine tests. In a small proportion of cases the disturbance was marked, and in one such case cochlear damage, giving rise to deafness, occurred. Both the vestibular and cochlear damage were irreversible.

Combined Streptomycin and P A S Therapy—The effects of combining streptomycin with P A S were investigated in 20 patients, 5 of whom had been previously treated by streptomycin. The remainder, 15 in all, had received general medical treatment without streptomycin. In each case the previous treatment had been given under the conditions of the M R C trial, and at the completion of the streptomycin or control period in every case further treatment was required.

On admission to the original trial, the cases had been classified in groups in the following proportions —

Group 1—Three streptomycin, four controls, total seven

Group 2—Six control cases

Group 3—Two streptomycin, three controls, total five

The two remaining cases, both controls, were classified as Group 5.

For the purposes of this investigation the results of the initial treatment in each group are compared with that of combined therapy. In each case streptomycin, 1 gm. daily intramuscularly in a single dose, was given for ninety days with P A S 15 gm. daily in divided doses.

Group 1—The 3 patients after treatment by streptomycin, remained tubercle positive. In one the pyelographic appearances of the affected kidney had improved. After observation for a period of eight months, the two in which no change had occurred developed cystitis and involvement of the other kidney. In one the original lesion had worsened.

Following combined therapy the first case showed further pyelographic improvement, the urine became negative for tubercle bacilli, and had remained thus for a period of six months. Of the two cases which had deteriorated, the cystitis had improved in both, in one the contralateral kidney had become tubercle negative, and the affected kidney was removed. Three months later the urine was tubercle negative, the remaining kidney normal and no cystitis was present, this having been maintained for twelve months. In the third case the contralateral kidney remained involved and further worsening of the original renal lesion had taken place.

Summary—In the above, following combined therapy, one case showed further improvement which has been maintained for six months. In another the bladder and contralateral kidney were improved and surgery for the original lesion resulted in improvement, which has been maintained for twelve months. The course of the disease was not arrested in the last case.

Control Cases—Of the 4 cases, all remained tubercle positive, one had developed cystitis and the remainder involvement of the other

kidney In one of the latter, the original lesion had worsened and a minor lesion developed in the contralateral kidney

TABLE I

Group 1 Streptomycin Cases After 8 Months' Observation

Total	Urine Conversion	Cystitis Developed	Involvement of Other Kidney	Pyelographic Changes		
				I	W	U
3	0	2	2	I	I	I

After S and P A S

Total	Urine Conversion	Cystitis		Other Kidney			Pyelographic Changes		
		Imp	None	I	U	NS	I	W	U
3	I	2	I	I	I	I	I	I	I

I = Improved, W = Worsened, U = Unchanged, NS = No spread

After combined therapy, three were tubercle negative Of these one showed pyelographic improvement but has failed to return for follow-up examination The others showed no pyelographic improvement

TABLE II

Group 1 Control Cases at the Completion of 3-6 Months' Control Period

Total	Urine Conversion	Cystitis Developed	Involvement of Other Kidney	Pyelographic Changes		
				I	W	U
4	0	I	3		I	3

After S and P A S

Total	Urine Conversion	Cystitis		Involvement of Other Kidney			Pyelographic Changes		
		Imp	None	I	U	NS	I	W	U
4	3	I	3	2	I	I	I		3

I = Improved, W = Worsened, U = Unchanged, NS = No spread

and partial nephrectomy was undertaken Thereafter urine conversion in both cases has been maintained for over six months The



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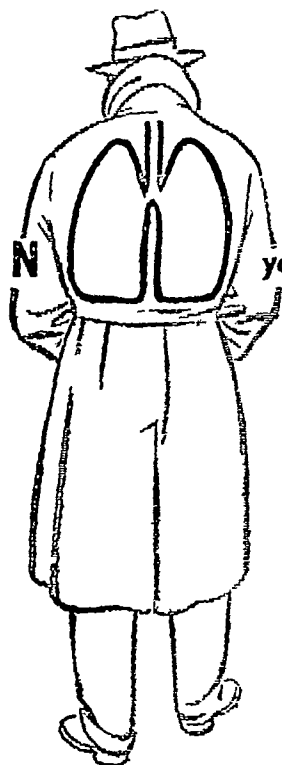
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fourth case, which remained tubercle positive, had shown bilateral pyelographic lesions following the control period

Summary—Of 4 cases, urine conversion was attained in three, pyelographic improvement in one, no change occurred in the last case

Group 2—Of the 6 patients in this group all remained tubercle positive following a control period. No improvement in the degree of cystitis was noted and in two involvement of the other kidney had occurred

After combined therapy all became tubercle negative at the completion of treatment, the cystitis had improved in every case and no involvement of the other kidney was detected

TABLE III

Group 2 Control Cases at the Completion of 3 6 Months' Control Period

Total	Urine Conversion	Cystitis			Involvement of Other Kidney
		Improved	Worsened	Unchanged	
6	.			6	2

After S and P A S

Total	Urine Conversion	Cystitis			Involvement of Other Kidney
		Improved	Worsened	Unchanged	
6	6	6			

Summary—Marked improvement occurred in all cases and is maintained to the present, a period varying from two months in the last case to fourteen months in the earliest case

Group 3—Of the 5 cases in this group, two had been treated by streptomycin, but both remained tubercle positive after treatment. In one the remaining kidney was improved but no improvement in the degree of cystitis resulted. In both, bladder contracture had commenced

After combined therapy the lesions of the remaining kidney in both cases were improved. One became tubercle negative, the other remained tubercle positive until the sixth month after treatment. The urine conversion has been maintained in both for a further six months. The degree of cystitis was difficult to assess as a result of increasing bladder contracture

Summary—The renal lesions in both cases were improved, urine conversion occurred at the completion of treatment in one case and in the other on the sixth month after treatment

Controls—Three cases all remained tubercle positive, no change was observed in the degree of cystitis and the lesion of the remaining kidney had worsened in one case

After combined therapy three were tubercle negative, the degree of cystitis and the disease of the remaining kidney were improved in each case. At subsequent examination, after twelve months, one had become tubercle positive and deterioration of the renal lesion had occurred.

TABLE IV

Group 3 Streptomycin Cases at Completion of Treatment

Total	Urine Conversion		Cystitis Unchanged	Other Kidney	
	Bladder	Kidney		Improved	Unchanged
2	0	1	2	1	1

After S and P A S

Total	Urine Conversion		Cystitis Unchanged	Other Kidney	
	Bladder	Kidney		Improved	Unchanged
2	1	2	2	2	

A second case has remained tubercle negative for fourteen months, but the filling defect in the affected kidney has reappeared. Repeated cultures of urine, however, have failed to show tubercle bacilli. In the third case no obvious disease was detected in the remaining kidney.

TABLE V

Group 3 Control Cases at Completion of Control Period

Total	Urine Conversion		Cystitis			Other Kidney		
	Bladder	Kidney	I	W	U	I	U	W
3					3		3	

After S and P A S

Total	Urine Conversion		Cystitis			Other Kidney		
	Bladder	Kidney	I	W	U	I	U	W
3	3	3	3			3		

The urine remained tubercle negative but progressive bladder contracture necessitated uretero-colic anastomosis. At operation a specimen of the kidney urine was obtained and found to be free from tubercle bacilli.

Summary—Three cases after treatment were improved, urine conversion was maintained in one for twelve months. The other two remain tubercle negative to the present, a period of fourteen months and six months.

Group 5—Two patients were selected for this group, in one of whom the disease was advanced. After the control period both cases remained tubercle positive, in neither had the cystitis improved nor had pyelographic changes occurred.

After combined therapy one case was tubercle negative, the cystitis had improved but no pyelographic improvement was noted. This has been maintained for six months. In the other case the advanced bilateral lesions remained unchanged and rapidly progressive bladder contracture took place.

TABLE VI

Group 5 Control Cases at Completion of Control Period

Total	Urine Conversion	Cystitis		Pyelographic Changes—None
		I	U	
2	0		2	2

After S and P A S

Total	Urine Conversion	Cystitis		Pyelographic Changes—None
		I	U	
2	1	1	1	2

I = Improved, W = Worsened, U = Unchanged

Summary—Two bilateral cases were treated, the worse showed no improvement, the less severe became tubercle negative and has remained so for the past six months.

CONCLUSIONS

The results obtained, following treatment by combined therapy of the patients in this series, cannot be strictly compared with those of the streptomycin treated cases. Of the 20 patients treated, 5 of these had received streptomycin at an earlier date, the remaining 15 general medical treatment. However, with this imperfect basis for comparison, the case for combined therapy appears slightly better. As in the case of streptomycin the established caseocavernous lesion responds poorly to treatment. In 5 cases treated by combined therapy, however, urine conversion was attained, in 2 cases partial nephrectomy was performed.

during this tubercle negative phase and the conversion has been maintained for six months. In one the lesion in the solitary remaining kidney was well established. The urine in this case was rendered free from tubercle bacilli for a period of twelve months. In the remaining 2 cases the lesions became shut off. In one of these it has remained thus for six months, in the other the constriction has regressed after fourteen months but the urine remains tubercle negative.

Combined therapy appears to afford a greater degree of protection to the contralateral kidney than does streptomycin. In all cases in which spread to the other kidney was displayed by the presence of a tubercle positive urine, without an obvious pyelographic lesion, urine conversion was attained. In other respects the results obtained were similar to those of the streptomycin treated cases. It should be borne in mind, however, that every case, in both the M R C trial and in the above group, received general sanatorium treatment and, where indicated, an operation was performed. It follows then, that neither streptomycin nor combined therapy is an alternative to prolonged sanatorium care or to surgery where conditions are favourable.

Ljunggren has recently carried out a follow-up of patients operated upon for renal tuberculosis at the hospitals of Stockholm from 1934 to 1943. The results have yet to be presented in detail, but Ljunggren considers that the endeavour to improve the results of treatment by early diagnosis and early operation has not met with the success which was anticipated. He suggests that early diagnosis should be followed by strict sanatorium treatment, chemotherapy and when the disease is in a more quiescent phase, surgery.

As to the choice of chemotherapeutic agent, Ljunggren has attained some measure of success using P A S alone for prolonged periods. Lloyd, Baumrucker and Stonington (1948) consider that streptomycin by itself has a very limited value and is not curative where there is a positive pyelogram. In early tuberculosis, however, where the pyelogram is negative, it is considered to be of great benefit.

Lattimer *et al* (1948) using streptomycin 1.8 gm daily for 120 days obtained a good response in early renal lesions, but where the renal disease, as shown by pyelography, is marked, the author considers that nephrectomy should be performed.

In my opinion it is not unreasonable to expect an enhanced result from a combination of both drugs. The small series of patients treated in Robroyston Hospital in this fashion offers some evidence in support of this.

Ross *et al* (1951) has reported in a review of 51 cases the effect of (1) streptomycin, (2) streptomycin and P A S, (3) streptomycin and P A S alternatively, (4) streptomycin, P A S and thioparamizone. In this series the best results were attained using methods (3) and (4).

Lane (1951) has reported a series of 52 cases, 9 of whom received streptomycin and moogral, the remainder streptomycin and potassium

iodide The latter is believed to promote solution and absorption of caseous material exposing masked tubercle bacilli to the influence of the streptomycin A 48 per cent conversion rate is claimed Streptomycin and potassium iodide is considered the most promising combination The most marked success was attained in those patients in whom the urine from the solitary remaining kidney contained tubercle bacilli, but in whom no obvious renal lesion was demonstrated This type of case has also responded well to streptomycin alone, and to streptomycin and P A S as reported above It may, however, be of some significance that the cases treated by Lane, in the above series, were not subjected to sanatorium regimen

In 11 of the 52 patients treated, calcification of the kidney was noted In only one of these was urine conversion attained, this patient reverted to positive after one year The author concludes that in the presence of calcification, even to a minimal extent, success is most unlikely

Lane has also reported the success of bladder instillations in the treatment of patients in whom tuberculous cystitis has persisted after nephrectomy The substance used is designated B 53 It is a soap derived from a branched fatty acid used in 0.5 per cent water solution buffered to pH 7.2 In patients with cystitis and spread to the remaining kidney, local treatment proved unsuccessful

A preliminary report on B 283 is included This drug, a phenazine dye, was given orally to 8 patients An immediate conversion rate of 50 per cent is reported, but in half of these relapse occurred, leaving a conversion rate of 25 per cent at the time of the report

In this brief communication the work performed at Robroyston Hospital has been detailed, and reference has been made to the conclusions of other workers By many the chemotherapy of renal tuberculosis may be condemned by the multiplicity and diverse combinations of drugs employed The variety of reagents subjected to investigation is, however, an index of the increasing ambition on the part of both surgeon and tuberculosis physician to solve the problem of renal tuberculosis

Chemotherapy has been shown to have positive value in the treatment of early renal tuberculosis, to offer some degree of protection to the contralateral kidney, and to improve the bladder in secondary tuberculous cystitis following nephrectomy In addition, though the incidence of post-operative dissemination in renal tuberculosis is low, it is significant that no such occurrence has been reported in patients receiving chemotherapy

It is becoming increasingly obvious that the majority of workers in this field are discarding the doctrine of immediate nephrectomy for renal tuberculosis From the time of diagnosis the patient should receive sanatorium treatment, under the supervision of a tuberculosis physician, the latter working as an integral part of a urological team

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RENAL TUBERCULOSIS

ITS PATHOGENESIS AND MANAGEMENT IN PATIENTS WITH EXTRA-UROGENITAL DISEASE

By WALTER M BORTHWICK, Ch M

Robroyston Hospital, Glasgow

IN my talk this afternoon, I intend dealing with the problem of renal tuberculosis, occurring firstly, as the only obvious manifestation of tuberculosis, and secondly, as a lesion coincidental to other obvious clinical disease. I do not intend, however, to make that distinction a sharp one, but I shall try to give the most recent views on the pathogenesis of renal tuberculosis and our ideas in Robroyston Hospital with regard to the management of the patient with renal and extra-urogenital tuberculosis. I shall also try to show that renal tuberculosis is more common than many suspect, and I am convinced that success in a campaign against this disease rests to a great extent on the tuberculosis physician, who is often in a position to initiate the investigation and diagnose the condition in its pre-clinical stage at a time when chemotherapy is likely to be most beneficial. As in all forms of tuberculosis, the sanatorium regimen is still the mainstay in treatment, and any tendency to dissociate the tuberculous patient from a sanatorium or a tuberculosis hospital for any part of his treatment, I feel, is a retrograde step.

For some statistical details on renal tuberculosis I have abstracted the case records of the last 200 patients in Robroyston Hospital suffering from that disease. These patients have all been in hospital within the last three years, but the time element is of no importance since no follow-up will be given.

TABLE I
Age Incidence in 200 Patients with Renal Tuberculosis

Age in Years	-10	-15	-20	-25	-30	-35	-40	-45	-50	-55
Number (Females)	1	4	12	23	14	10	5	2	3	1
Number (Males)	3	5	22	23	33	16	14	3	2	4
Total	4	9	34	46	47	26	19	5	5	5

Females, 75

Males, 125

Read at a meeting of the Tuberculosis Society of Scotland held at Bangour Hospital on 25th January 1952

The age incidence can be seen from Tables I and II. The incidence in females seems to be higher than in males in the earlier age groups, but in both sexes over 85 per cent of the cases occurred between 16

TABLE II
Percentage Incidence in 200 Patients

Age in Years	16-25	16-30	16-35	16-40
Female	46.7	65.3	78.7	85.3
Male	36	62.4	75.2	86.4
Total	40	63.5	76.5	86

and 40 years of age. The higher incidence in males has been a constant feature since a definite genito-urinary unit was established in Robroyston Hospital in 1934 and up to date the reason for this has eluded us. I shall be grateful for any suggestions on this finding.

TABLE III
Incidence of Extra Genito-Urinary Tuberculous Lesions (200 Patients)

Total	Number with other Lesions	Per Cent
125 (Males)	52	41.6
75 (Females)	36	48
Combined Males and Females	88	44

TABLE IV
Localisation of Extra Genito-Urinary Lesions

Site	Males	Females	Total
Lungs	23	6	29
Lungs and Bone	8	3	11
Lungs and Joint	5	5	10
Glands	0	5	5
Bone	10	11	21
Joint	5	5	10
Multiple	1	1	2

The incidence of clinical extra-urogenital disease in these patients was 44 per cent (Table III), and the localisation of these lesions can be seen in Table IV.

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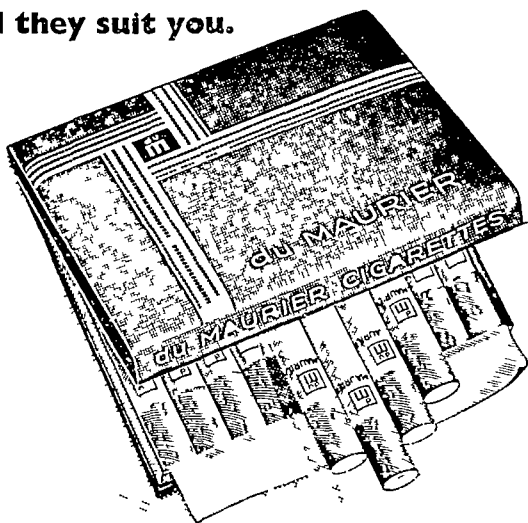
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I tried to find out the sequence of events in the tuberculosis history of the 88 patients who had extra-urogenital disease, but accurate details were only possible in 64 instances (Table V). As far as could be ascertained the renal lesion was diagnosed from one to over ten years after the other tuberculosis manifestations.

TABLE V

Interval (in Years) between Extra-Urogenital Lesions and Diagnosis of Renal Tuberculosis (64 Patients)

Time in Years	1	2	3	4	5	6-10	10+
Number	11	10	12	6	4	15	6

An obvious difficulty here is my lack of follow-up to see how many of the 200 patients will develop lung or bone and joint disease. It is, however, a very definite impression that the number of patients with renal tuberculosis who subsequently develop a pulmonary or bone lesion is very small. I shall try to give a possible explanation of this later.

The presenting symptom which initiated the urological investigation in these 200 patients (Table VI), was an increased frequency of micturition in 97 or just under half, pain in 9 (4.5 per cent), hæmaturia in 22

TABLE VI

Signal Symptom, if any, Causing Urological Investigation in 200 Cases of Renal Tuberculosis

Symptom	Increased Frequency of Micturition	Pain	Hæmaturia	Retention of Urine	None
Number	97	9	22	4	68

(11 per cent), and retention of urine in 4 (2 per cent). In the remaining 68 patients there was none of the generally recognised symptoms of renal tuberculosis, and the investigation was carried out after routine examination had shown tubercle bacilli in the urine or an unexplained pyuria or albuminuria (Table VII).

TABLE VII

Reason for Urological Investigation in 68 Symptom Free Patients

	Tubercle Bacilli in Urine	Albuminuria	Pyuria	Epididymitis
Females	10	5	2	
Males	5	1	1	44

Many of you know our ideas on the subject of genital disease in the male, and it is routine procedure to carry out a full urological investigation in these men. Forty-four of the 68 patients suffered from tuberculous epididymitis without any urinary upset, and one can almost say like Wells (1943), that epididymitis can be included in the symptomatology of renal tuberculosis in the male. That a very close association exists between renal and genital disease in the male is clearly demonstrated in Table VIII. Over 80 per cent of the 125 men had

TABLE VIII

Incidence of Genital Tuberculosis in 125 Males Suffering from Renal Tuberculosis

	Number	Per Cent
Combined Epididymal and Pelvic Genital Disease	83	66.4
Pelvic Genital Disease alone	19	15.2
Total	102	81.6

genital disease, 66.4 per cent having combined epididymal and pelvic genital disease and 15.2 per cent having pelvic involvement alone. I have no doubt that follow-up of the 19 men will show subsequent epididymitis in many of them.

The localisation of the kidney disease when first diagnosed (Table IX), was unilateral in 154 and bilateral in 46. The frequency of involvement of right and left kidney was the same. In these cases

TABLE IX

Localisation of Kidney Disease —

Right Kidney—77

Left Kidney—77

Both Kidneys—46 (12 excretory bacilluria)

Localisation of Kidney Disease in 68 Symptom free Patients —

Right Kidney—23

Left Kidney—27

Both Kidneys—18 (11 excretory bacilluria)

with bilateral involvement the disease was definite and sometimes advanced in 34, while the remaining 12 had tubercle bacilli in both kidney specimens but no disease was demonstrable in the urograms. With regard to the 68 symptom-free patients, the disease was bilateral in 18 instances, in 7 of which moderate to advanced lesions were found. Eleven patients in this group had tubercle bacilluria. Medlar (1926, 1932) and Band (1935, 1943) have proved that the isolation of tubercle bacilli from the kidney urine means that there is a renal lesion.

From the above findings a point worthy of stress and not always realised, is that renal tuberculosis may be bilateral and advanced without any urinary symptoms. In point of fact the only true symptoms

of renal tuberculosis are hæmaturia arising from the kidney and very occasionally renal pain. The commonest symptom, as quoted, increased frequency of micturition, is not really a symptom of renal tuberculosis but a symptom of vesical disease, and that may develop soon after the start of open renal tuberculosis some years later or not at all. Most textbooks on this subject stress the general symptoms with which one associates an early tuberculous lesion elsewhere in the body. The loss of weight, appetite and lassitude and other symptoms of tuberculous toxæmia are all given an important place in the diagnosis of renal tuberculosis. In our experience, these signs and symptoms occur as the exception rather than the rule in patients who do not have any extra-urogenital tuberculous disease. Toxæmia from a renal lesion seems to be minimal, and I would be interested to hear any observations on the reason for this. When the bladder becomes involved then the increasing frequency of micturition during the day and night has its effect on the general well-being of the individual. Even when epididymitis develops, apart from the initial upset lasting days rather than weeks or months, the patient usually shows little evidence of toxæmia. It has long been recognised in Robroyston Hospital that the patients who are under treatment for renal tuberculosis without any other tuberculous disease are by far, apparently, the healthiest patients in the hospital. Even in progressive renal disease, in the absence of very marked vesical irritability, that well-being may continue until most of the renal tissue is destroyed and the patient approaches a uræmic condition. Weight, blood sedimentation, appetite, blood urea and general examination may all remain normal until a short time before the onset of uræmia. One obvious exception to this is the pyonephrotic kidney, which produces a marked reaction in all these tests in the individual.

To sum up this section, I would stress the importance of a full urological examination in tuberculous patients who have albuminuria or pyuria. Routine examination of the urine for tubercle bacilli will produce surprising results, while epididymitis demands a full examination. Hæmaturia, renal pain or increasing frequency of micturition are all well recognised as symptoms necessitating a urological investigation.

Since Medlar (1926, 1932) demonstrated by serial section that bilateral tuberculosis of a microscopic nature could be seen in the kidneys of many patients who had died of extra-urogenital tuberculosis, our conception of the origin of renal tuberculosis has developed. The primary complex in tuberculosis is usually in the lungs or intestines, and later that may be followed by a bacillæmia in which the organisms are carried to various parts of the body. Thereafter there is a latent period depending on the number and virulence of the organisms and the resistance of the host. According to Wallgren, quoted by Ljunggren (1951), if the infection develops near the serous membranes it usually manifests early, and later if the bones and joints are affected. The

kidney lesions develop still later. The earliest lesions in the kidney are usually bilateral and found in relation to the glomeruli of the cortex, constituting the sub-clinical phase. These lesions may heal or become encysted. If the former occurs it could account for a later unilateral or "surgical kidney," but if the latter happens, at any time reactivation due to re-infection may occur. As stated by Ljunggren, the cortical lesions may ulcerate into the renal tubules and give rise to tubercle bacilluria. At this stage pyuria may be absent or slight and urography will demonstrate normal function and outline. The cortical foci may spread directly or by lymphatics to the tubules of the pyramids and give rise to a definite lesion. The blood supply of the pyramid, especially in the papilla, is poorer than in the cortex, and the chances of healing are not so favourable. Healing foci in the papilla are rare, and instead there is a tendency to necrosis and cavity formation. When this has ulcerated into the renal pelvis, the infection can spread to the ureter, bladder, and in the male to the genitalia.

At this stage (Band, 1948), the renal pelvis has now become infected, and tubercles and ulceration occur in the lining membrane. Renal function is impaired and the renal pelvis becomes atonic. Residual urine which is present becomes reabsorbed, and tubercle bacilli pass in a retrograde manner to the tubular systems of the neighbouring calyces. Secondary foci then appear as confluent groups of tubercles in more distant zones of the renal cortex. This condition is often seen after nephrectomy, when the kidney, on section, may show cavitation in relation to the upper group of calyces and numerous tubercles in the cortex near the lower pole.

The hæmatogenous dissemination of tubercle bacilli is not limited to the kidneys, since renal tuberculosis and bone and joint lesions are frequently associated. Irrespective of the time of onset of these lesions, and I personally believe that the orthopædic lesion usually manifests itself earlier in the majority of cases, one must accept the fact that milary tuberculosis is much more common than most of us realise. We must regard milary tuberculosis as a quantitative rather than a qualitative conception, since it follows that milary tuberculosis not only occurs frequently but that in most cases it is relatively innocent in character. Apart from the possibility that clinical milary tuberculosis may arise, there is the alternative that pre-clinical milary tuberculosis is either cured or that it passes into chronic tuberculosis of the organs such as kidneys or bone and joint.

Another thought at this stage from the point of view of prognosis is, that whatever treatment is considered for unilateral renal disease, and nephrectomy is usually the method of choice, it must be remembered that the contralateral kidney nearly always has at least a minute lesion which may break down. Therein, I feel, lies a possibility for chemotherapy.

It is important to realise that the term renal tuberculosis has largely been superseded by the more accurate ones of genito-urinary or

urogenital tuberculosis These names recognise that we are dealing with a system-disease in which the kidney is usually the primary source, showing a great tendency to spread to other organs in the same system The resulting lesions often show a varied character in the different organs There can be small renal lesions with marked vesical disease There can be extensive bilateral renal tuberculosis without cystitis This varied response may also be evident in that nephrectomy for unilateral renal disease is sometimes followed by healing of vesical disease, while in others aggravation of the vesical condition occurs It is not infrequent to find in men with progressive and not long-standing genital disease, calcified lesions in the kidney or even calcification of the whole kidney Presumably the genital disease in most has been caused by a spread from the kidney, yet the stages of infection and response of the various organs has been so different Removal of the kidney does not influence genital disease

When renal tuberculosis is diagnosed in its symptom-free phase it does not always mean that it is diagnosed at an early phase Generally the disease is slowly progressive, so slow sometimes that many years may pass without obvious change in the affected individual That does not mean, however, that we can consider renal tuberculosis as a chronic, unimportant event in a tuberculosis case history This disease is a fatal one requiring sanatorium treatment when diagnosed, but the chronicity becomes important when the patient also suffers from extra-urogenital tuberculosis Close liaison between the surgeon and tuberculosis specialist is of highest importance in these cases and, if necessary, the deciding vote as to the general conduct of the case should lie with the tuberculosis physician

In Robroyston Hospital, beds are set aside for patients with renal tuberculosis, and on an average 40 to 50 patients are usually in residence at any one time The 200 patients about whom I spoke earlier were all in hospital within the last three years, some in fact being still there When possible, the unit consists of two sections, one male and the other female, situated in wards containing non-pulmonary tuberculous patients The presence of open pulmonary tuberculosis excludes the patient from the unit, and accommodation is found in a pulmonary ward

It is difficult to particularise with regard to our ideas on the management of the patient with multiple tuberculous lesions In general, I feel that progressive pulmonary or active bone or joint disease should have preference over active intervention in renal tuberculosis The watchword should not be early nephrectomy but nephrectomy during the most suitable period when other lesions are at least under control Chemotherapy has changed our ideas a little, and that will be discussed later, but even with chemotherapy it is advisable to control the extra-urogenital lesions before embarking on operative intervention There are exceptions, one of which I have mentioned before The pyonephrotic kidney, even in the presence of progressive pulmonary disease,

should be removed as early as possible. A frequency of micturition which disturbs the patient day and night to such an extent that the general condition suffers, should, if possible, receive treatment.

Disease of the smaller joints does not, as a rule, interfere with the management of a case. The larger joints, especially the hip, should, if possible, receive prior claim, since instrumental investigation and operative intervention may have a deleterious effect. Spinal tuberculosis also, should be in a quiescent phase, since theoretically the position at operation may cause damage, although in the more urgent operations on the urinary tract I have never recognised any such damage.

With regard to pulmonary tuberculosis, events can move with such rapidity and with such disastrous results that control of this disease should always be attempted before urological interference is undertaken. Close observation of the renal tract can be carried out without serious upset to a patient with active pulmonary disease. If instrumental investigation is considered inadvisable, and that is seldom, then rarely does intravenous urography do any harm.

I do not wish to give the impression that renal tuberculosis can be considered as an unimportant incident. The advanced stages of this condition cause probably more upset and discomfort than a similar period in almost any other tuberculous lesion. A frequency of micturition at five-, ten- or fifteen-minute intervals obviously makes life intolerable and everything possible should be done to prevent this or treat it. The point I would like to make is that in a patient with pulmonary and renal tuberculosis, when both conditions are suitable for treatment, then in my opinion, the pulmonary disease should receive prior claim, always provided that close watch is kept on the genito-urinary condition. It is only advisable to avoid nephrectomy until the lung lesion is under satisfactory control, not to wait until so-called healing has taken place. In the individual with untreatable pulmonary tuberculosis, then all necessary steps should be taken to treat coincidental renal disease to avoid undue suffering from bladder irritability.

Each case of urogenital tuberculosis should be under the supervision of the tuberculosis specialist in a sanatorium or tuberculosis hospital, and close liaison with the surgeon should exist so that the latter can carry out in the words of Cibert (1946) not "la néphrectomie précoce" but "la néphrectomie opportune."

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SOME UNUSUAL MANIFESTATIONS OF ABORTUS FEVER

By A W BRANWOOD, M D , F R C P E , M R C P

MANY physicians are of the opinion that abortus fever is rare in this country. It is very seldom diagnosed, although some workers are convinced that many cases of this disease exist and produce chronic ill health in the community.

Sir W Dalrymple-Champneys, in his Milroy Lecture of 1950, stated that undulant fever is a neglected problem in this country. He quoted only 983 cases in England and Wales during the past twenty years. Other authors have similar figures. There were no proved cases of abortus fever admitted to the Edinburgh Royal Infirmary from 1932-1936 and only occasional cases thereafter.

Dalrymple-Champneys has explained the small number of cases of brucellosis in this country as being due to (1) a general impression that abortus fever is a rare disease, (2) the diagnosis of abortus fever is too readily excluded by one negative agglutination, (3) the low mortality of this disease has not brought it to the public eye.

Another explanation is that abortus fever may mimic many other conditions and its mode of onset can be so unusual that the diagnosis of undulant fever may never be considered.

During the years 1942-1952 the author has seen 10 proved cases of brucellosis. In only 3 of these could the disease be described as typical. The majority of cases had a most unusual onset and the diagnosis was only made later. Once the diagnosis had been made, however, these cases could be divided into the ambulant, undulant, continuous or malignant groups, again illustrating the fact that a diagnosis of brucellosis can usually be made once one thinks of it.

CASE MATERIAL

The cases seen by the author occurred in Cheshire and in the Royal Infirmary, Edinburgh. In 7 of these cases it was the mode of onset which was misleading. They presented as (1) Meningitis, (2) Appendicitis, (3) Anæmia and Splenomegaly, (4) Pleurisy, (5) Hepatitis, (6) Rheumatism, (7) Gastro-enteritis.

(1) *Meningitis* —A veterinary surgeon aged 26 was admitted to hospital suffering from generalised aches and pains for about a fortnight. On the day of his admission he suddenly became drowsy and complained of intense frontal and occipital headache. He had neck rigidity and presented a typical picture of meningeal irritation. He had a furred tongue and sweated profusely. His temperature was 102° and he had tachycardia. The W B C was 6200 with an absolute lymphocytosis. He was not anæmic. Lumbar puncture

yielded clear cerebro-spinal fluid under reduced pressure with a slightly increased protein content and 16 lymphocytes per cmm. A provisional diagnosis of benign lymphocytic chorio meningitis or early T B meningitis was made. In view of the patient's occupation, however, an agglutination test for *B abortus* was performed. This was negative in dilutions of 1:16 upwards. The patient was treated with analgesics for his headache. He remained drowsy for two or three days during which time he ran an intermittent fever of 101°-102° F and then suddenly became afebrile, looked much better and stated that he now felt fit. A week later the patient was still afebrile but his spleen was now slightly enlarged. Another agglutination test for *B abortus* gave a positive agglutination of 1:256 upwards.

The patient admitted that recently he had been working in a bacteriology department making a vaccine for abortus fever, but as far as he knew had not inoculated himself.

(2) *Acute Appendicitis* —A farm worker aged 21 was admitted to hospital with symptoms of acute appendicitis. A laparotomy was performed and the appendix which appeared healthy was removed. Subsequent histological examination showed the appendix to be normal. Four days after his operation the patient developed flitting pains in all his joints and a severe pain in his left shoulder. The transient joint pains abated but the pain in the shoulder persisted. The patient had a low grade pyrexia of 100°-101° F and profuse night sweats. His white blood count was 6000 with 55 per cent lymphocytes. The B S R was 22 mm per hour. Agglutination for *B abortus* was negative in dilutions of 1:16 upwards. The patient was given full doses of salicylates and his temperature became normal. His left shoulder was still painful and there were still night sweats. X-ray of the chest showed no evidence of pulmonary tuberculosis. At this time the spleen became palpably enlarged. In view of the symptoms and signs a provisional diagnosis of undulant fever was made in spite of a negative agglutination test. The patient was given aureomycin and the profuse night sweats stopped in two days. The shoulder became less painful and the patient looked and felt better. He was discharged a fortnight later, the agglutination reaction for *B abortus* being still negative. He was seen again in 6 weeks' time. He had kept perfectly fit during this period. The serum now showed agglutination to *B abortus* up to 1/512.

Although this patient was a farm worker he stated that as far as he knew no cattle on the farm were diseased nor had there been any "spontaneous abortion" among the herd.

(3) *Anæmia and Splenomegaly* —A girl of 12 was admitted to hospital with a complaint of frontal headache, intermittent epistaxis and sore throat of a few days' duration. She stated that for several weeks prior to this she had felt weak, easily tired, breathless on exertion and had sweated profusely at night. On examination she looked pale and tired and far from healthy and had a nocturnal pyrexia of 101°-102°. Her spleen was palpable. The blood picture was as follows —Hæmoglobin 70 per cent, R B C 4,000,000, C I 0.87, W B C 4200 with 54 per cent small lymphocytes, 40 per cent polymorphs, 6 per cent monocytes and 2 per cent eosinophils. Sternal puncture showed a normoblastic marrow. An X-ray of the chest was normal and the Widal reaction and a blood culture were negative. A provisional diagnosis of a reticulosis, perhaps Hodgkin's disease, was made and the patient was treated symptomatically. At weekly intervals blood cultures, Widal and Paul Bunnell reactions and agglutination for *B abortus* were performed. For

three successive weeks these were all negative. During this time the patient gradually improved—the sweating became less, the temperature returned to normal and she looked and felt much better. There was an increase in her weight and her hæmoglobin was now 88 per cent. There was still a leucopenia, however, and the lymphocytes remained above 55 per cent of the total W B C. The liver and spleen were smaller although still palpable. At the end of a month the agglutination tests were again repeated and on this occasion the serum agglutinated *B abortus* up to dilutions of $1/512$ and a week later agglutination of *B abortus* was obtained in dilutions of $1/1024$.

The patient was seen again 3 months later. She was very fit and not anæmic. The spleen was no longer palpable. The white blood count was 6000 per c mm but with still 40 per cent lymphocytes. The serum still agglutinated *B abortus* in dilutions of $1/1024$.

This girl lived in the country and told us she drank a lot of milk.

(4) *Jaundice*—A man of 23 had complained of anorexia, general malaise and attacks of shivering for a week. This was followed by a frontal headache and the gradual onset of jaundice. On examination this young man had mild jaundice, a very furred tongue and a soft tender liver which was enlarged to two finger breadths below the costal margin. The spleen was enlarged to percussion. The stools were pale and the urine contained bile and urobilinogen. The temperature varied between 97° F and 100° F. The white blood count was 4600 with 48 per cent lymphocytes. A cephalin cholesterol flocculation test showed $[++]$ (2). The patient was thought to be suffering from infective hepatitis and was treated accordingly. After about 14 days the jaundice had disappeared, there was no bile in the urine although there was still urobilinogen, and the liver was just palpable. The cephalin cholesterol was $[+]$ (1). The spleen was now definitely palpable. In spite of the disappearance of the jaundice the patient, contrary to expectation, felt no better. His tongue was heavily coated. He developed profuse night sweats and the temperature persisted. There was still a leucopenia and a lymphocytosis. A Widal reaction was negative but the serum agglutinated *B abortus* in dilutions up to $1/512$, and 4 days later the serum gave a positive agglutination to *B abortus* up to $1/1024$.

This man was a town dweller and there appeared to be no obvious source of infection in this case.

(5) *Rheumatic Fever*—Undulant fever may often cause arthritis and in some instances it can be mistaken for rheumatic fever, as is seen in the following case.

A man of 46 years, a dockyard worker, had suffered from a mild attack of "influenza" three weeks previously. He apparently recovered from this and then, ten days later, suddenly complained of severe pains in all his joints. This symptom was accompanied by profuse sweating and a temperature of 101° F. He had a tachycardia and was diagnosed as a case of acute rheumatism. The joint pains did not improve when the patient was given massive doses of salicylates, indeed the man appeared worse. His temperature varied between 97° and 100° F. The sweating persisted, especially at night. The white blood count was 4800 with 57 per cent of lymphocytes. The B S R was only 32 mm per hour. His spleen, not palpable on admission, became enlarged three days later. Undulant fever was suspected and the serum agglutinated *B abortus* in dilutions up to $1/256$.

This man could give no explanation as to how he might have acquired the

disease although he had been helping to unload a cattle boat four weeks previously

(6) *Pleurisy and Pericarditis*—A girl of 18 years, previously healthy, suddenly developed severe substernal pain which radiated into the neck. She was admitted to hospital. On admission the temperature was 102° F, her B S R was 97 mm per hour and there was a tachycardia of 102 per minute. Pericardial friction was audible over the whole of the præcordium. The patient was diagnosed as a case of acute rheumatic pericarditis and was given massive doses of salicylates. Her tachycardia persisted and the temperature fell to 99° F. The friction rub persisted. Five days later the temperature suddenly rose to 104° F and she complained of pains in most of the larger joints. The white blood count at this time was only 3200 with 50 per cent lymphocytes. The pericarditis remained and there was now a left-sided pleurisy. The temperature became hectic, swinging from 97° F to 105° F. The patient was desperately ill and sweated profusely. Her blood culture and all agglutination tests, including *B abortus*, were negative. Penicillin was administered purely empirically with absolutely no effect. The patient developed a small left-sided pleural effusion. The aspirated fluid was serous and sterile. She was given streptomycin with no improvement. At the end of a fortnight the temperature fell and remained normal. The pericarditis and pleurisy had cleared up. An electrocardiograph and X-ray of the chest were normal. The white blood count was only 4000 and there was still a lymphocytosis. She also had a mild hypochromic anæmia. Fourteen days later she again complained of pains in the shoulder and hip joints and the temperature rose to 105° F. The drenching sweats returned. In three days' time everything had once again returned to normal. She now had splenomegaly and agglutination for *B abortus* was positive in dilutions up to 1/256. The patient was treated with aureomycin with a very dramatic improvement.

This girl although residing in a town had just returned from a holiday in the country prior to the onset of her symptoms. She denied any contact with infected cattle or indeed drinking an excessive quantity of milk.

(7) *Gastro-enteritis*—A man aged 63 was admitted to hospital with a history of the sudden onset of colicky abdominal pain, diarrhoea and vomiting. For several days he was sick after everything he ate and the diarrhoea was very troublesome. He developed a frontal headache during this period and his temperature varied between 97° F in the morning and 102° F at night. He was treated symptomatically as a case of gastro-enteritis. After five days he felt better and the diarrhoea had stopped although he still complained of headaches in the evening when his temperature was elevated. Examination of the abdomen on admission revealed generalised tenderness which rapidly improved *pari passu* with his condition. The spleen, however, then became palpable. At no time was the white blood count higher than 5000 and there was a persistent lymphocytosis of 53 per cent. The Widal reaction was negative and there was no agglutination of *B typhosus* or *B paratyphosus* A or B in serum dilutions of 1/16 upwards. Bacteriological examination of the stool revealed a normal flora. Three days later the agglutination tests and Widal reaction were repeated, again with negative results. The patient's serum was also tested against *B abortus* and agglutination was obtained in dilutions 1/16 to 1/512. Twelve days later agglutination was obtained with *B abortus* in dilutions of 1/16-1/1024.

Throughout this period, once the acute gastro-intestinal symptoms had spontaneously abated, the patient felt perfectly fit but still had a pyrexia at night. He was treated with *B melitensis* vaccine and the temperature gradually returned to normal.

This patient was a gardener and, although a countryman, stated he had not been in contact with diseased cattle nor had he drank any more milk than the rest of his family who were all well.

The above cases illustrate some of the ways in which undulant fever may present. It can be seen how easily some of these cases of abortus fever may be misdiagnosed and, due to a spontaneous remission, be entirely missed, only to lead to chronic ill health at a later date. It cannot be too strongly emphasised that brucellosis must always be kept in mind in the differential diagnosis of many conditions.

There are several points about brucellosis that are well worth consideration.

(1) *Ætiology*

Evans and other workers, including Fitch and Dubois, have shown that the disease can be transmitted to humans by goats, sheep, swine, cats, dogs and horses. The recognised source of infection in Britain, however, seems to be mostly bovine, although horses suffering from fistulous withers may transmit the disease to humans. Individuals become infected by drinking raw milk or eating milk products from the milk of infected cattle.

It is very unlikely that butter and cheese transmit the infection, for the lactic acid of the sour milk is bacteriocidal for the brucella organisms. Butter and cheese, however, if freshly made, may contain a few organisms and thus act as a source of infection.

Direct contact with infected animals or their carcasses or excreta may also provide a route of infection. Garrod has demonstrated that of all the intestinal pathogens, brucella is the most susceptible to the acid gastric juice. It is often stated that a period of ill health or some short acute illness, where there may be a temporary associated achlorhydria, precedes the initial attack of undulant fever. In only one patient in this series, the man diagnosed initially as rheumatic fever, was there any history of some previous ill health before the onset of his symptoms. It is suggested therefore that people in good health do not become infected by the brucella abortus.

In only one patient in this series, the veterinary surgeon, was there any possibility of tracing the infection. There was a possibility of contact infection in the dock worker who had recently helped to unload a cattle boat. One of the other patients worked on a farm, and three more were country dwellers, but no history of any mode of infection was present in these cases other than the possibility of drinking raw milk.

These few cases illustrate very well one of the features of this disease, namely, its sporadic occurrence and, in many cases, complete absence of any apparent source of infection.

(2) *Sex Incidence*

Many workers have stressed the difference in sex incidence of this disease. Brucellosis is far more commonly seen in men than in women. This may be occupational, although other factors seem to play a part in determining this sex incidence. In this series there were 5 men and 2 women. The ages of the men varied from 18 to 65 years. The two females were aged 12 and 18. Magoffin *et al* in their series of abortus fever found that 78 per cent were males, but stated that in the age groups under 13 and over 35 the sex incidence was approximately the same. Olin and Taylor had similar results, and the latter suggested that females after puberty seem to be relatively immune to abortus fever or at least to clinical attacks of this disease. This apparent immunity may disappear after the menopause, for the incidence of the brucellosis is the same in both sexes over the age of 65 years.

CLINICAL MANIFESTATIONS

Undulant fever usually has an insidious onset. In the majority of patients the symptoms are increasing tiredness, lethargy, occasional headaches and sweating. It is when the onset is sudden and dramatic that the condition is so often missed, for in these cases the disease may mimic practically anything. Dalrymple-Champneys has stated that when the onset is sudden the presenting symptoms may resemble a variety of conditions from pneumonia to melæna.

The very few cases in this series show how diverse are the clinical features of abortus fever and how sudden the onset may be.

Most authors have classified the disease into the five well-known types, namely, the ambulant or mild, the undulant or ordinary type, the intermittent, continuous and the malignant variety. Yet because the onset may be sudden and the condition at first undiagnosed it is sometimes difficult to fit the disease into one of these five types.

Sweating is the most frequent and severe symptom. In these cases drenching sweats were a marked feature of every one. This sweating, however, may be only mild or moderate. Nevertheless, be this symptom mild or severe it always occurs in the late afternoon or at night and is accompanied by a very characteristic sour smell which should be almost diagnostic of the undulant fever.

Tiredness and lethargy are complained of bitterly during the height of the fever, only to disappear when the temperature is normal. This state of well-being, insisted on by the patients during their apyrexial periods, is again almost pathognomonic of brucellosis.

Headache is a noticeable feature. In some instances it can be so severe that the condition is mistaken for meningitis, as in the case in this series. Hughes in 1897 mentions a patient who, having been ill for several weeks, developed symptoms of cerebral irritation, and at post mortem *B melitensis* was isolated from the meninges. Lemaire

studied several non-fatal cases of brucella meningitis and pointed out the similarity of meningitis due to brucellosis and tuberculous meningitis. Thereafter other workers, including Desage, Magnani and Roger, described similar cases and stressed the difficulty of diagnosis between tuberculous and brucella meningitis.

Pain is another common complaint. It is usually situated in the joints. In most cases only one or two joints may be involved. In some patients, however, the disease can begin suddenly as in the man in this series, with acute polyarthritides and may easily be mistaken for rheumatic fever. The pain may also be present in the muscles, especially of the back or the abdomen. In the latter case the sudden onset of abdominal pain leads to a mistaken diagnosis of acute appendicitis in many patients.

Respiratory symptoms are also encountered. These may vary from the symptoms of bronchitis to those of an acute pneumonia. Pleurisy was present in one girl in this series.

Cardiac Manifestations

Rennie and Young in 1936 first described endocarditis due to a brucella in this country, and Hardy *et al* reported similar cases in the American literature. Since then other cases have been recorded in Scandinavia, America and Great Britain. One patient in this series suffered from both pleurisy and pericarditis. Pericarditis has been described by Dalrymple-Champneys in one case of undulant fever.

Splenomegaly—This sign is invariably present at some time in every case of brucellosis. Indeed it is one of the most important diagnostic features of this condition.

Hepatomegaly—Enlargement of the liver is not so commonly present as splenomegaly. In some cases the liver may be slightly tender and, rarely, the presence of jaundice may lead to a mistaken diagnosis of infective hepatitis. This happened in one patient in this series.

Anorexia, constipation and diarrhœa are symptoms encountered frequently during the course or onset of the disease. If diarrhœa occurs at the onset the patient may be treated symptomatically for gastro-enteritis and again the condition can be missed.

Rigors are said to be a frequent feature of abortus fever. The only patient with this manifestation was the girl with pleurisy and pericarditis. Malaise with slight shivering, however, were early symptoms in many of the other patients.

Various *skin manifestations* have been described in undulant fever, but they are neither characteristic nor specific for this condition.

General Ill Health—Many American and Canadian authors have described a condition of chronic brucellosis. Griggs and Scarlett maintain that in the United States and Canada chronic ill health previously explained by "rheumatism," septic foci or even neurosis

are really due to brucellosis. These patients have no acute episodes and show no positive agglutination tests. These workers state that although brucella infection cannot be proved at the time, a positive agglutination is found years later.

General fatigue accompanied by neurosis or even psychosis due to abortus infection are encountered in this country. Hausmann and Schenken described a melitensis meningo-encephalitis in a patient who had been ill for a year with general fatigue, headaches, attacks of delirium and subjective sensory phenomena. The infective organism was the porcine variety of brucella.

Depression and apathy, an important feature of brucellosis, may be due to the long-continued fever with its periods of remission and inevitable relapses or may perhaps be explained by organic changes in the central nervous system.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of brucellosis covers so wide a field in medicine—for the disease may resemble practically any condition from P U O to depressive psychosis—that it will not be considered further. It cannot be stressed enough, however, that in any disease where the symptoms are prolonged and the clinical features perhaps a little unusual a brucella infection must always be considered.

DIAGNOSIS

An absolute diagnosis is often difficult to make, and in many cases is only made by surmise. The diagnosis can be made by obtaining a positive culture, a positive agglutination test and, as stated by many workers somewhat ironically, a "typical" clinical picture.

(a) *A Positive Culture*—This diagnostic procedure is not often performed in this country. During life a positive culture may be obtained from blood, urine, faeces, sternal marrow, tonsillar swab or vagina. If a suitable medium is used and the atmosphere contains an increased content of carbon dioxide, then with repeated subcultures organisms can be grown. McCullough states that daily blood cultures for 7-10 days will yield a positive result in patients in whom the disease is suspected. Cultures can also be obtained post mortem from the spleen, bile and lymph glands.

(b) *Agglutination*—A negative agglutination does not rule out a diagnosis of brucellosis. The test should be repeated frequently and a positive result may be obtained when the acute phase of the disease is over and the patient is in a remission. In some cases the agglutination is persistently negative and may only become positive years later. Furthermore, the test can only be a true criterion if the antigen used is satisfactory. Prozones may be present and thus give a false negative agglutination. Positive agglutination of sera in a dilution of 1 : 256 and a rising titre thereafter is proof of the diagnosis.

(c) *A "Typical Clinical Picture"*—The least said about this the better. Whatever the clinical manifestations, however, the blood picture in brucellosis is invariably the same. There is always a lymphocytosis. This can be either absolute or relative. Dalrymple-Champneys has suggested that the degree of lymphocytosis bears a relationship to the agglutination titre of the patient's blood. An absolute lymphocytosis is usually found when the serum is agglutinated in dilutions of 1:1000 or more. Certainly a persistent lymphocytosis is a constant finding in this condition and indeed should suggest the diagnosis.

SUMMARY

Several cases of abortus fever are described to illustrate the many and unusual ways in which this disease can present. It is suggested that a large number of cases are missed, often being mistaken for other conditions. The incidence of brucellosis in the community is thus higher than is realised. Indeed many workers through the ages have stated this fact. Hippocrates in 278 B.C. described a prolonged fever with sweating and tendencies to relapse as "the abortus epidemicus". Wilson, in 1932, suggested that if the reduction factor obtained by the relative frequency of agglutination of the typhoid group and *B. abortus* by sera submitted for Widal reaction be applied to the annual notifications of typhoid fever this would give an approximate idea of the incidence of *B. abortus* infection. On the above basis the incidence of brucellosis would be about 400-500 per annum.

Although the ætiology of this condition is well known it is difficult, in the majority of patients, to trace the source of infection or indeed explain the sporadic incidence of the disease. It is suggested that a period of ill health or debility may predispose to the infection.

Brucellosis must always be considered in any disease with prolonged fever or where the clinical manifestations are somewhat unusual.

The advent of aureomycin offers a permanent cure to the majority of these patients. Thus the incidence of brucellosis with its trail of chronic ill health and acute periods of relapse can be lessened provided the physician is fully aware (a) that abortus infection does occur in this country, (b) that it may mimic many other conditions, and (c) that the disease can be diagnosed by repeated blood cultures or agglutination tests.

The dictum, "Was man weiss sieht man", applies in abortus fever just as in any other condition.

I wish to thank Professor Murray Lyon for the use of some of this case material.

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NOTES

At the Annual Meeting of the College, held on 22nd October 1952, the following Office-Bearers were elected for the ensuing year —

Royal College of Surgeons of Edinburgh	President, Professor Walter Mercer Mr W Quarry Wood J J Mason Brown, OBE Professor R C Alexander, CBE, Mr K Paterson Brown, Mr John Bruce, CBE, Mr Arthur J C Hamilton, Mr James S Jeffrey, Mr Archibald Brown Kerr, OBE, TD, Sir James R Learmonth, KCVO, CBE, Mr Robert Mailer, Dr David S Middleton, TD, Mr T McWalter Millar, Dr Douglas Miller, Mr R Leslie Stewart Henry Wade, CMG, DSO Jackson Hartley, OBE OBE	Vice-President, Secretary and Treasurer, Mr President's Council, Pro- Conservator of Museum, Mr James Norman Convener of Museum Committee, Mr John Bruce, Librarian, Dr Douglas Guthrie
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At a meeting of the Royal College of Surgeons of Edinburgh, held on 22nd October 1952, Professor Walter Mercer, President in the Chair, the following who passed the requisite examinations were admitted Fellows

Amirali Abdulkarim Alidina, MB, BS UNIV BOMB 1948, Gurbux Singh Babbar MB, BS UNIV PUNJAB, 1936, Keith Loraine Barnes, MRCS ENG, LRCP LOND 1940, Alastair Kingsley Brown, MB, CHB UNIV EDIN 1941, Jitendrarao Vajendrarao Desai, MB, BS OSMANIA MED COLLEGE, INDIA, 1942 Sami Salim Khoury, MD UNIV BEIRUT, 1946, Manjiah Khudabux, MB, BS UNIV BOMB 1948, Herbert Kramer, MB, BS CH UNIV WITWATERS-RAND 1947, Robin Campbell Wilson Lowe, MB, CHB UNIV EDIN 1945, John Donald Malloch, MB, CHB UNIV EDIN 1944, Naizby Noble, MRCS ENG, LRCP LOND 1943, Richard Douglas Oatway, MD UNIV MANITOBA, 1942, Francis Ferenc Sandor, MD UNIV BUDAPEST 1930, LRCP & S EDIN (TRIPLE) 1952, Lionel Arthur Scrivin, MB, CHB UNIV NEW ZEAL 1941, Gurmukh Singh Sekhon, MB, BS UNIV LAHORE, 1943, John Robert Sinha, MB, BS UNIV PATNA, 1934, MS UNIV PATNA, 1944, John Robert Smith, MB, CHB UNIV GLASG 1945, David Michael Stevens, MB, BS UNIV LOND 1944, Neil Patrick Stracey, MB UNIV CALC 1946, Shelton Edgar Wijetilaka, MB, BS UNIV CEYLON, 1946

NEW BOOKS

Diary of a Psychiatrist By JAMES T FISHER, MD, and LOWELL S HAWLEY
 Pp 256 London Medical Publications Ltd 1952 Price 16s net

In this book Dr Fisher tells the story of his life which started with farm work, cattle ranching, and dealings in real estate. Eventually, however, he became interested in Medicine and graduated at Harvard. He explains that he was not interested in Surgery and thought that under such circumstances Psychiatry was the logical answer for his life work. In this book he gives the fruit of his labours and experience. His story is told in an interesting and sometimes in an amusing manner, but unfortunately he does not add to our psychiatric knowledge or understanding. It cannot be considered a serious contribution to psychiatric literature.

Portrait of a Hospital By WILLIAM BROCKBANK Pp 218, with 56 illustrations and 3 maps London Wm Heinemann 1952 Price 25s

Two hundred years have passed since the institution which was to become the Royal Infirmary of Manchester first opened its doors. It was a house "with twelve beds and all other conveniences". Among the original members of the Staff was Charles White, surgeon and obstetrician, who was later to achieve world-wide fame. To the original hospital no patient was admitted who "could pay for his own cure", and a recommendation signed by a subscriber was essential. At that time Manchester was a small town, but its growth was very rapid, especially during the nineteenth century. The "house" was soon replaced by a new Infirmary containing 80 beds, built at a cost of slightly over £2500. Extensions and new wings were added, and in 1766 a "lunatic hospital" was built. Another early requirement was met in 1779 when Public Baths were erected close to the Infirmary. The Royal Patronage was accorded in 1830, and 1831 Queen Victoria paid her first visit to Manchester and inspected the building, but the centenary of the great institution in the following year does not appear to have been the occasion of any celebration. With the march of progress the infirmary became obsolete and even unhealthy, accordingly a scheme of reconstruction was commenced, and various improvements were made. "The Great Infirmary Controversy" regarding the future dragged slowly on, and it was not until 1909 that an entirely new building was opened by King Edward VII, on a site adjacent to the old hospital which was then demolished. To this magnificent new Infirmary many additions have been made, and the heavy damage caused by enemy action has been made good. It is a hospital of which the city may well be proud, and the story of the 200 years of its service is well and clearly told by Dr Brockbank. The book is beautifully produced, the plans and illustrations are of much interest and artistic merit, and, apart from the letterpress they give a clear idea of the progress of the hospital. So noble a theme deserves a good chronicle, and this book well supplies it.

Surgical Gynecology By J. P. GREENHILL, M.D. Pp 350, with 101 multiple illustrations. Chicago The Year Book Publishers, Inc. 1952. Distributed in Britain by Interscience Publishers Ltd. Price 65s (price to subscribers to the whole series of Handbooks of Operative Surgery, 60s.)

Surgical Gynecology is the second volume of a planned series of Handbooks of Operative Surgery. It is designed for "young gynaecologists, general surgeons and those physicians in general practice who also perform operations". After a useful section on pre-operative and post-operative care written by Dr Loeff, there follow the author's technical descriptions of operations. These are illustrated, step by step, by Miss Angela Bartenbach's line drawings. A few non-gynaecological operations, which it may be found necessary or desirable to perform in the course of the gynaecologist's work, are included. No attempt is made to discuss the indications for employing the procedures described, or to assess the relative merits of alternative methods of operative treatment.

The descriptions so far as they go are clear, but in a few instances there is a tendency to oversimplification. For example, abdominal myomectomy deserves more elaboration and the technique of dealing with a large interstitial cervical fibroid should be included. Guidance in overcoming the difficulties encountered when faced with adherent pelvic masses due to inflammation or endometriosis is limited. Also more help could be given in just how to define the uterine artery, how to open the ureteric canal and how to expose the obturator fossa in a radical hysterectomy. Apart from plate 72, when a posterior incision mysteriously becomes located anteriorly, the illustrations are excellent and well reproduced. Their number no doubt accounts for the high cost of this handbook, but this method of multiple illustration is undoubtedly the best to use when "writing up" operations.

NEW EDITIONS

Synopsis of Tropical Medicine By Sir PHILIP MANSON BAHR Second Edition
Pp xiii+248, with 7 plates London Cassell and Company 1952 Price
15s net

Costing the price of thirty oranges, this pocket size Synopsis answers most questions on Tropical Medicine. An addition to the valuable plates records the discovery of the malaria parasite's base in the liver. Space is found for Insecticides, for the revolution in the treatment of Plague, Typhus and Enteric by the use of Antibiotics, for the Sulphone treatment of Leprosy (omitting the DDS regime), for the drugs tried in seeking something better than tartar emetic in schistosomiasis, for the warning against Stilbamidine's toxicity.

The suggestion for treating thread worms with barium meals catches the eye but one misses mepracrine amongst the anthelmintics for thread as well as for tape worms, and daraprim and acetarsol amongst the remedies for malaria and balantidiasis.

Scottish missionaries to Calabar will be glad to find here the modern treatment for the "eye worm."

By making marginal notes as new knowledge appears those who use this Vade-Mecum would find an easy way of keeping up to date.

Principles of Human Physiology (Starling) By Sir CHARLES LOVATT EVANS,
DSC, FRCP, FRS, LL.D. Eleventh Edition Pp xii+1210, with 709
illustrations London J & A Churchill 1952 Price 52s 6d

"Of course, like all text books, the book is patchy, superficial and out of date, patchy because it represents a menu based on my desultory reading and on current fashion, superficial, when seen from the view point of research workers, in each narrow field. But it does represent in summary the Principle of Physiology as I understand it." Thus with charm and conciseness Sir Charles Lovatt Evans reviews his own work in the preface. Suffice it to add that the book distills the ripe experience of the best all round physiologists in Britain to day. The uniform elegance of style and the integrity of outlook in this one man textbook more than compensate for inevitable weaknesses of detail. The serious student of physiology (both graduate and undergraduate) will probably find this the most useful book for his shelf, both for reference purposes and to dip into at odd moments.

Surgical Anatomy By C. L. CALLANDER Third Edition, edited by BARRY J
ANSON, M.A., PH.D., and WALTER G. MADDOCK, M.S., M.D., F.A.C.S. Pp xi+
1074, with 929 illustrations London W. B. Saunders Limited 1952
Price 70s net

The need for a Third Edition of this considerable volume within nine years is evidence of its popularity in the United States. As a consequence of the untimely death of the original author, the present revision has been undertaken by Anson and Maddock, the respective professors of Anatomy and Surgery in the Northwestern University Medical School of Chicago.

The volume retains much of its original pattern and, as before, is beautifully produced, and lavishly illustrated by nearly a thousand drawings, diagrams, and photographs. The lack of colour in the illustrations is a disadvantage, and for a text of surgical anatomy, too many of the figures are of purely pathological or surgical interest.

Nevertheless, the present edition will be valuable to young surgeons and to those studying for the higher surgical diplomas, to whom the innumerable and well illustrated operative techniques will undoubtedly be educative.

BOOKS RECEIVED

- ANDERSON, W A D, M A, M D, F A C P Synopsis of Pathology Third Edition (*Henry Kimpton, London*) 60s net
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The Transactions of the Medico-Chirurgical Society of Edinburgh

DYSPHAGIA WITH SPECIAL REFERENCE TO CARDIOSPASM

By JAMES M GRAHAM, Ch M , LL D , F R C S Ed

IT is usual for the retiring President to offer to the members, in the form of a valedictory address, some reflections on a subject of his own choosing. With the latitude allowed on these occasions, I have ventured to choose a clinical subject and will refer to certain of the conditions which cause dysphagia and particularly to cardiospasm and the late results of treatment for this condition.

The surgery of the œsophagus scarcely existed in my early days. Recent advances date from the publication in 1913 by Thorek of his account of the first successful removal of a carcinoma of the thoracic œsophagus. His patient not only survived the operation but lived for thirteen years without recurrence.

My own interest in this branch of surgery dates from 1917, when, in the absence of my chief, Professor Alexis Thomson, I was called upon to undertake the list of operations. Amongst the cases was one recommended by Dr Logan Turner, who was present at the operation. It was an epithelioma of the hypopharynx involving the upper end of the œsophagus. I had not seen such a case operated on and had no knowledge of the technique required. After removal of the affected segment it was impossible to reconstitute the gullet, and it was necessary to leave the upper end of the œsophagus anchored in the neck. It was only by a combination of good fortune and beginner's luck that the patient not only made a good recovery but has remained well ever since. I have ventured to mention this case again as it is certainly unusual to be able to report a case operated on for malignant disease, particularly in this area, alive and well thirty-four years after operation (Fig 1).

Since then I have operated on other cases of this kind, and in 1926 I had the opportunity for the first time of performing the plastic operation recommended by Wilfrid Trotter by which the defect in the gullet was repaired by a skin flap. Good fortune attended this case too, for I am happy to record that Mrs J is still alive and well, swallowing

Valedictory address by the President, read at a meeting of the Medico-Chirurgical Society of Edinburgh on 24th October 1951

normally, twenty-five years after removal of an epithelioma of the hypopharynx. Of the 16 cases in which this operation was completed, 3 lived long enough to be regarded as cured.

Few if any of these cases have been operated on in recent years. It is worth considering whether there is not still a place for operation in cases of carcinoma of the hypopharynx in preference to treatment by irradiation. Professor McWhirter informs me that he has a record of 91 cases of carcinoma of the hypopharynx treated by X-ray therapy in the Royal Infirmary, of this number 4 are still alive at intervals of from four to twelve years after the treatment.

My former house surgeon, Dr T. M. Prosser, now on the staff of the Westminster Hospital, informs me that at that hospital between 1935 and 1947 there were 56 cases of post-cricoid cancer treated of which 53 have been followed up. These cases were all treated by gamma irradiation on the 4-gram telerradium unit and some in addition had at the same time high voltage X-ray treatment. Fifty of the 53 patients followed up had died in less than three years and 3 patients had survived for periods of from five to sixteen years.

It is obvious that carcinoma of the hypopharynx is not very radio-sensitive, and I am inclined to think that operation should be recommended in the first place when removal of the disease appears to be feasible. The case with advanced disease should still be treated by irradiation. If, as is probable, there is no satisfactory evidence of immediate regression, operation could still be considered in a proportion of these cases.

I should like now to mention the first case of pharyngeal pouch on which I operated, as it illustrates a rare complication. The patient, Mr S., an elderly gentleman, had struggled on for many years until he was unable to swallow anything. He was fibrillating and in such poor condition that he was fit only for a gastrostomy in the first instance. Two weeks later diverticulopexy, the first stage of a two-stage operation for removal of the pouch, was performed. After the operation the patient developed pneumonia and an empyema for which drainage was required. The second stage of the operation was indefinitely postponed as the patient's symptoms were completely relieved by the high fixation of the pouch. There was, however, a limit to the good fortune in this case, as six years later he returned with an epithelioma which had begun in the pouch and was already inoperable and involving the skin. The case emphasises the importance of removal of the pouch which is essential as a rule for complete relief of symptoms.

Recent advances have now made it safe to remove the pouch in one stage. The only occasion when a two-stage operation may still be advisable is in the case of a very large pouch extending into the mediastinum, for there is always a chance that leakage will occur a few days after the operation (Fig. 2).

A similar but much rarer type of diverticulum occurs in relation to the lower third of the oesophagus, projecting usually to the right, a short

distance above the diaphragm. It is commonly referred to as an epiphrenic diverticulum. A patient, Mr MacD, aet 55, with this type of diverticulum, had been under observation for ten years before operation for its removal seemed justified. There was no real dysphagia and the patient complained mainly of discomfort due to distension of the pouch which could be relieved by washing it out with an œsophageal tube. When the symptoms became more persistent three years ago, an operation for its removal was undertaken by the transpleural route on the right side. The pouch, which was about the size of a goose's egg, was removed without difficulty. No leakage followed the operation. The patient made a good recovery and has remained well (Fig 3).

CARDIOSPASM

The main facts regarding cardiospasm are well known. It is of interest mainly because of the doubtful ætiology and in regard to the problems of treatment.

(1) There is marked dilatation and hypertrophy of the œsophagus without organic stenosis.

(2) The lower end of the œsophagus from the hiatus in the diaphragm to the cardiac orifice appears to be normal.

(3) There is no paralysis of the œsophageal wall, for irregular and sometimes excessive peristalsis occurs and the muscle coats are hypertrophied.

(4) Some form of neuro-muscular disorder is obviously responsible for the obstruction to the passage of food immediately above the cardia.

There is no anatomical sphincter at the lower end of the œsophagus. Knight has shown, however, that the circular muscle coat from the level of the hiatus to the cardia acts as a physiological sphincter which is controlled by the vagus and the sympathetic. That the arrest in the passage of food in cardiospasm is due either to spasm or to failure of relaxation of the physiological sphincter is proved by the fact that the obstruction is relieved by division of the circular muscle fibres in this area. The absence of any sign of hypertrophy of the circular muscle fibres seems to me to confirm Hurst's original suggestion that the condition present is an achalasia or failure of relaxation rather than spasm.

That local and persistent spasm of non-striated muscle in the alimentary tract leads to gross hypertrophy I have seen in the colon. In a male patient, aet 60, with diverticula of the pelvic colon, localised spasm at the site of the diverticula led to such a degree of muscle hypertrophy that a tumour-like mass formed which closely simulated a malignant tumour and caused almost complete obstruction of the colon. As a result of the rest following colostomy, the muscle hypertrophy so completely disappeared that at a subsequent laparotomy no trace of the supposed tumour could be found and the colostomy was closed. The patient remained well for five months after closure of the colostomy, but gradually thereafter the symptoms of obstruction recurred, and when

the patient was readmitted to hospital it was found necessary to perform a colostomy again. The cause of the obstruction was again found to be due to a tumour in the same situation, similar in every way to the tumour previously observed. The patient died after the operation, and at the post-mortem examination it was shown by the late Dr James Dawson that only drops of water could be forced through the obstructed area. The tumour proved on naked-eye and microscopical examination to be formed solely by a gross hypertrophy of the fibres of the circular muscular coat associated with the presence of minute diverticula.

High bilateral vagotomy in the cat causes a condition resembling cardiospasm in man. In the absence of vagal function the tone of the physiological sphincter persists, the œsophagus dilates and fills with food and the animal slowly starves. That the tone is maintained by the sympathetic was proved by Knight (1934-35a) when he showed that after vagotomy division of the sympathetic fibres to the lower end of the œsophagus was followed by relaxation of the sphincter and complete relief of the obstruction to swallowing.

In recent years bilateral vagotomy has frequently been performed for the relief of symptoms due to duodenal and anastomotic ulcers. Following this operation, the patient may suffer considerable discomfort from loss of gastric tone and occasionally complains also of slight temporary dysphagia. There is no suggestion, however, that cardiospasm is due to a lesion either central or peripheral of the vagi, all the evidence points to the vagi being normal in these cases.

Hurst suggested that the neuro-muscular imbalance with apparent sympathetic over-activity might be due to a lesion of the ganglion cells of Auerbach's plexus. It is known that these ganglion cells form a cell station in the vagal pathway. The absence or the loss of these cells could be expected to interfere with the vagal impulse. Following Hurst's suggestion, Rake (1927) of Guy's Hospital examined several early specimens of achalasia and stated that the ganglia in the lower part of the œsophagus showed inflammatory changes or were even replaced by fibrous tissue.

The problem was investigated by Lendrum (1937) working with material from the Mayo Clinic. He examined in great detail a series of thirteen specimens which had been collected over a period of years. While stressing the wide variation in the number of ganglion cells in the normal œsophagus, he recorded a striking loss or a complete absence of the ganglion cells in Auerbach's plexus in all his cases of cardiospasm. Some support for the theory that a reduction in ganglion cells is responsible for the changes in cardiospasm is afforded by the facts recently established in connection with Hirschsprung's disease of the colon. It has been shown that the ganglion cells of the myenteric plexus are absent from the rectum and pelvic colon distal to the dilated loop. Unfortunately Hirschsprung's disease and cardiospasm, with many features in common, are not strictly comparable, for there is no

evidence that cardiospasm is congenital as true Hirschsprung's disease definitely is

The main difficulty in settling the facts regarding the integrity of the ganglion cells in cardiospasm is due to the lack of specimens available for examination. I was aware of only two specimens in the Anatomical Museum of the University which I used to demonstrate to my class of surgical pathology many years ago. One of these is of historical interest as it was presented by Dr Alexander Wood over a hundred years ago and was described by him in the *Edinburgh Medical Journal*, it has been sufficiently preserved for microscopical examination. Professor Drennan of the Pathology Department has provided other four specimens, one of which was from a case of my own, and these have been examined by Dr Rae Lyon, to whom I am indebted for the following report

*" Examination of Ganglia at Cardio œsophageal Junction
in 5 Cases of Cardiospasm*

" Using slight modification of Lendrum's technique where the ganglia cells were enumerated in a measured vertical strip of œsophagus immediately adjoining the stomach, 5 specimens were examined and compared with a control series which had 7.89 ganglion cells per cm

" The oldest, though it had been preserved for a very long time, had fully retained the histological features and details, yet neither ganglia nor any traces of ganglia cells were observed

" The second case, with hypertrophy and dilatation of the œsophagus, had 11.3 ganglion cells per cm

" A specimen from Mr Graham's own series had two adjacent blocks of tissue examined, one had 12.6 ganglion cells per cm, the other had only 4.6 ganglion cells per cm

" One section was taken from a case of syphilitic aortitis to demonstrate leukoplakia and hypertrophy of the œsophagus. Only three ganglia could be discovered which gave an average of 0.8 ganglion cells per cm

" Finally, at a recent autopsy the hypertrophied œsophagus was examined in three separate sites and in each there were over ten ganglion cells per cm

" Thus, in comparing the 5 cases with the normal obtained from a control series, ganglion cells were reduced or absent in 2 specimens, 2 had more than the average number of cells and from the final case adjacent strips gave one result above normal, and the other below

" Conclusions

" 1 In this limited series the constant reduction or absence of the ganglion cells of Auerbach's plexus reported by Lendrum and others has not been observed

" 2 Except in the oldest specimen, no stretches of œsophagus, devoid of ganglia, were discovered, nor were there present dense nerve bundles, such as were found by Bodian, indicating that there is no direct relationship between cardiospasm and Hirschsprung's disease

" 3 Though this series is small, the cases appear to be divisible into groups with an average number of ganglion cells and those with a marked reduction

" 4 The great variation in ganglion cell counts, even between serial sections, suggests that unless innumerable sections are cut, this method of investigation has no great accuracy in assessing the number or condition of the ganglia in Auerbach's plexus "

Although a reduction in the ganglion cells of Auerbach's plexus in cardiospasm is an attractive theory, it must be admitted that the evidence so far produced is inconclusive and that the cause of cardiospasm is still uncertain

DIAGNOSIS

This can usually be established easily by the history and the characteristic X-ray appearances of the œsophagus. An œsophagoscopic examination should settle any doubtful problems

X-RAY EXAMINATION

In a typical case the œsophagus is dilated and fusiform in outline with the lower end at the level of the diaphragm. In advanced cases the degree of dilatation is excessive. Peristalsis is active in the earlier stages while at the same time irregular and ineffective. The regular waves which follow the act of swallowing tend to fade as they pass downwards and fail to reach the lower end. In the lower two-thirds of the œsophagus the normal waves are frequently replaced by irregular contractions and by superficial waves of tertiary type. These irregular contractions tend to persist and to recur unlike the peristaltic waves in the normal œsophagus which correspond only to individual acts of swallowing. When dilatation is very marked, only momentary tertiary waves are likely to remain and these may finally cease. The smooth fusiform outline of the dilated œsophagus reaching to the level of the diaphragm, the irregular peristalsis and the limited passage of barium and in addition the absence of the usual gas bubble in the stomach are characteristic of the condition.

DIFFERENTIAL DIAGNOSIS

Although the diagnosis can usually be established easily, an œsophagoscopic examination should be carried out as a routine, it is essential when the diagnosis is doubtful and is required in most cases as a preliminary to treatment by dilatation. The short history and steady deterioration of the patient's condition usually suggest the cause of the dysphagia in cases of carcinoma. When the dysphagia is due to carcinoma, the œsophagus is seldom greatly dilated and there is no great retention of food as in cardiospasm. In most cases of carcinoma of the lower end of the œsophagus and of the cardiac end of the stomach the diagnosis is obvious on X-ray examination. Occasionally the appearance of the dilated œsophagus in cardiospasm may be simulated by a localised carcinoma of the cardiac end of the stomach which has



FIG 1 —Mrs M Thirty four years after removal of an epithelioma of the hypopharynx, showing the œsophagus implanted in the neck



A



B

FIG 2 —Large pharyngeal diverticulum A Before operation, B showing the first stage



A



B

FIG 3—Mr MacD Case of epiphrenic diverticulum A Before, and B after removal



A



B

FIG 4—Mr M A Dilatation of the œsophagus with dysphagia due to peptic ulceration
B The same case showing peptic ulceration and a hiatal hernia.



A



B

FIG 5—Mrs B Case of cardiospasm A Before, and B after treatment with a Negus dilator The œsophagus is reduced in size but still shows some irregular peristalsis



FIG 6—J F Case of cardiospasm fifteen years after treatment by manual dilatation Complete relief of symptoms with a gain of 5 stones in weight Œsophagus still dilated with some irregular peristalsis



A



B

FIG 7—Mrs N Case of cardiospasm A Before, and B after oesophago gastrostomy, showing still some dilatation of the oesophagus



A



B

FIG 8—G M Case of cardiospasm A before, and B after Heller's operation The oesophagus is restored almost to a normal size and the symptoms are completely relieved



A



B

FIG 9—J McD Case of cardiospasm A Before, and B after Heller's operation Symptoms completely relieved but still slight delay in emptying and tertiary waves present Gas bubble present after operation

infiltrated the lower end of the œsophagus without producing a filling defect on radiological examination

A case of dysphagia, referred to me by Dr Greig Anderson as a probable carcinoma of the cardiac end of the stomach, illustrated the difficulty occasionally met with in determining the diagnosis. The appearance of the X-ray plate suggested cardiospasm and an œsophagoscopy examination was inconclusive as it had not been possible either to pass the œsophagoscope through the cardia or to obtain a positive biopsy. A further X-ray examination of the patient in the Trendelenburg position confirmed the clinical diagnosis of carcinoma and a transpleural resection was successfully performed. It is interesting to note that this patient from whom more than half of the stomach as well as the lower end of the œsophagus was removed five years ago, has recently suffered from a hæmatemesis due to peptic ulceration at the lower end of the œsophagus. A test meal in this case shows that there is an absence of free HCl in the resting gastric juice but that later free HCl appears, no doubt as a result of the action of hormonal secretion from the pyloric end of the stomach. It is instructive to know that free HCl can still be secreted in a case of carcinoma of the stomach after an extensive resection when both vagi have been divided.

If a diagnosis of cardiospasm is sometimes suggested by the X-ray appearance of the œsophagus in a case of carcinoma, I have also known cases in which through inadequate investigation the opposite mistake has been made and carcinoma has been diagnosed instead of cardiospasm. A middle-aged woman appeared in my out-patient clinic many years ago and asked to have her gastrostomy tube changed. The operation of gastrostomy had been done elsewhere five years before for a supposed carcinoma at the lower end of the œsophagus. Œsophagoscopy examination showed that a moderate degree of cardiospasm was present and the instrument was easily passed into the stomach. After adequate dilatation the patient was able to swallow normally and later the gastrostomy was closed. Contrary to expectation, the patient was far from grateful. It appeared that she was a gypsy travelling the country with a show, and that she used to entertain the public with some sort of a performance with her gastrostomy tube, posing as "the woman with the rubber stomach." She seemed to regret that her source of livelihood had been removed.

There is seldom any difficulty in differentiating simple strictures. Occasionally in cases of peptic ulceration at the lower end of the œsophagus the patient will complain of difficulty in swallowing and it will be necessary to distinguish this cause of dysphagia from carcinoma or cardiospasm. The dysphagia due to œsophagitis or peptic ulceration may be mainly or entirely due to spasm, but in chronic cases there is the possibility of an organic stenosis as a result of fibrosis. X-ray examination will show moderate dilatation of the œsophagus with a stenosis some distance above the diaphragm with smooth walls tapering fairly rapidly. In most cases a hiatal hernia is present, and it is possible

when sufficient barium has entered the stomach and the patient is recumbent with the head lowered, to demonstrate the presence of a pouch of stomach above the level of the diaphragm. The œsophagoscope and a biopsy will settle the diagnosis in almost all doubtful cases.

My first case of peptic ulcer of the œsophagus in which a clinical diagnosis was made illustrates the extreme degree of dysphagia which may be due to œdema and spasm without organic stenosis. The case was referred from a medical ward in 1936.

Mr M, aet 50. Dysphagia without pain had been present for three months, and for two weeks the patient had been unable to swallow anything. The radiologist had examined the patient some weeks before and had reported a malignant stricture. He had been œsophagoscoped a few days before I saw him and the preliminary report seemed to confirm the diagnosis—later it was reported that the tissue removed was inflammatory. After a gastrostomy the patient's capacity for swallowing gradually returned and a fresh X-ray examination revealed the presence of an ulcer crater and a hiatal hernia (Fig 4). After eighteen months the gastrostomy tube was removed as the ulcerated area had healed. The patient has remained well, he has symptoms of a duodenal ulcer and suffers occasionally from heartburn, but has had no recurrence of dysphagia.

TREATMENT

Treatment by dilatation should be employed in every case in the first instance. The day of the mercury bougie is past. Experience shows that the sphincteric area can be most satisfactorily stretched by a hydrostatic dilator in the form introduced by Plummer at the Mayo Clinic and by Negus in this country (Fig 5).

Approximately 70 per cent of the cases are symptomatically cured by dilatation with one or other of these instruments. According to Olsen, Harrington, Moersch and Andersen (1951) of the Mayo Clinic, satisfactory results are obtained in 75 per cent of cases and only 20 per cent cannot be relieved permanently by dilatation. Maingot (1949) has found operation necessary in 10 per cent of cases treated with the Negus dilator. Johnstone and Wooler (1949) state that in a series of 46 cases treated by the Negus dilator 35 patients were completely relieved of dysphagia while in 8 cases the treatment failed or was unsatisfactory. Success with these forms of dilator depends upon the successful rupture of the circular muscle fibres at the lower end of the œsophagus. There is a risk, although a small one, of rupture of the œsophagus.

The indications for operation can be defined as failure of dilatation to relieve the symptoms or when it is impossible to introduce the dilator.

Mikulicz Operation—Till recently the most popular operation was digital dilatation of the lower end of the œsophagus introduced by Mikulicz in 1904. The success of the operation depends upon the stretching and rupture of the muscle fibres at the narrow lower end of the œsophagus. The operation, however careful the technique, is not an aseptic one.

I have performed the operation in 5 cases. One patient died after the operation. He was too exhausted for almost any form of surgical interference. At the post-mortem examination the cardia was found to be successfully dilated and there was no rupture or sepsis. One of my patients gained 5 stones in weight and has remained free of dysphagia for fifteen years (Fig 6). The dysphagia returned, however, in 2 of the cases. There are no indications now for this operation as its objects can be more safely achieved by other means.

Sympathectomy (Knight's Operation)—From his experimental work, Knight (1934-35b) suggested that a sympathectomy below the diaphragm should be tried in cardiospasm. Mr W A D Adamson was the first to perform this operation and his case was a brilliant success. I tried Knight's operation in 2 cases, both of which were failures. Other surgeons have had the same experience. The failure of the operation is no doubt due to the fact that the sympathetic nerve supply to the lower end of the œsophagus in man is much more extensive than in the experimental animal. Professor Mitchell of Manchester, while still attached to the Anatomy Department in Aberdeen, showed that in addition to the branches of the coeliac plexus the lower end of the œsophagus receives many branches from above the level of the diaphragm. I think the subsequent history of Mr Adamson's case suggested to him the probability that the dysphagia had been due to peptic ulceration and spasm. The patient undoubtedly had an ulcer diathesis and the stenosis in the œsophagus was some distance above the diaphragm.

Œsophago-gastrostomy Cardioplasty—These operations have frequently been performed in recent years, particularly in the United States. In most cases the operation has been performed by the transpleural route.

With this route the new or enlarged opening remains above the level of the diaphragm and not only the sphincteric control at the cardia but the pinch-cock action of the diaphragm is lost. When the cardia becomes incompetent in this way, acid contents tend to regurgitate from the stomach, particularly when the patient is lying down, and peptic ulceration is likely to occur in the lower end of the œsophagus.

Recently Barrett and Franklin (1949-50) have reviewed the results of their cases including 17 cases of œsophago-gastrostomy and 6 cases of cardioplasty. The immediate results of their operation were excellent. The main object of their paper, however, was to draw attention to the unsatisfactory late results and to condemn these operations. In their experience these operations often produce more serious symptoms than the original condition, and they attribute the harmful results entirely to the free communication between the stomach and the œsophagus. After a period of from three to six months symptoms appeared in most of their cases, such as pain, bleeding, anæmia and recurrence of dysphagia. Of 17 cases in which the operation of œsophago-gastrostomy had been done, only 3 were well and relieved of their previous

symptoms My own experience of œsophago-gastrostomy is limited to one case which in regard to the subsequent history was similar to the cases recorded by Barrett and Franklin

Heller's Operation—This operation corresponds closely to Rammstedt's operation for congenital pyloric stenosis As originally described by Heller in 1913, the circular muscle coat of the œsophagus in the constricted area was divided by vertical incisions on both anterior and posterior aspects A single anterior incision has since been found to be adequate The operation has been practised to a considerable extent in France, but is seldom referred to in American literature In this country it has been employed as the method of choice in recent years by Barlow, Maingot and Allison It can be performed either by the abdominal or the transpleural route Like most general surgeons, I have used the abdominal route The operation can be completed safely and as a rule easily through an abdominal incision Thoracic surgeons prefer the transpleural route and this method should certainly be selected when difficulty in exposure of the cardia below the diaphragm is anticipated The circular muscle fibres are thin and the greatest care is needed to avoid puncturing the mucosa The incision for division of the muscle fibres should extend from a point immediately on the gastric side of the cardia to the point where the dilatation of the œsophagus begins at the upper level of the hiatus in the diaphragm The retraction of the circular muscle coat on each side is much greater than would be expected, and a wide area of mucosa is exposed so thin that the contents can be seen moving within the lumen of the œsophagus

Results of Heller's Operation—There is sufficient evidence from records published in recent years to prove that the immediate effects of Heller's operation are satisfactory It is important to know what the late results are likely to be In this connection I have some evidence to offer for my cases have been reviewed on two occasions, almost four years ago and again recently when Mr Gilmour and Dr MacKenzie of the Radiology Department kindly examined the patients for me

The operation was performed in 13 cases One patient died following the operation The fatal case was a man of 36 who had twice previously been operated on for the same condition He had been treated by sympathectomy below the diaphragm and by Mikulicz's operation He was much relieved by the digital dilatation but the dysphagia recurred and he was admitted to hospital three years later in poor condition The operation was difficult owing to adhesions The patient did well for forty-eight hours but then collapsed and died following the perforation of a gastric ulcer Such an unusual complication could not occur in a straightforward case

The remaining 12 cases have been available for review In one case, Mrs N, the division of the muscle fibres was incomplete and much too limited and the operation necessarily failed to relieve the symptoms

Before the division of the circular muscle fibres was completed, a

small tear appeared in the exposed mucosa as a result of traction on the stomach. The closure of the opening was perhaps more thorough than was needed. To make certain that there would be no leakage, the divided muscle was sutured together again.

It was surprising that the patient was completely relieved of dysphagia for some months. When the symptoms returned, no relief was obtained with a hydrostatic dilator and a transpleural œsophago-gastrostomy was performed (Fig 7). Again the dysphagia was completely relieved but only for a time, as œsophagitis developed as described by Barrett and Franklin.

Fortunately her symptoms are at present in abeyance and for a period of a year she has been well apart from slight anæmia, and has been free of dysphagia.

In December 1946, 10 of the cases were examined and X-rayed, at intervals of from one year to four years after Heller's operation. All of the patients were in good condition and well, with an average gain of 2 stones in weight. All were able to take a full normal diet. None had had any difficulty in swallowing and no regurgitation had occurred in any of the cases (Fig 8). The fact that there is no tendency to œsophagitis and peptic ulceration after Heller's operation was confirmed in this series of cases at this time and during the later review. The patients without exception were well pleased with the result of the operation and very grateful for the relief obtained.

The same cases have recently been reviewed again, together with one additional case operated on three and a half years ago. The operation had been performed over eight years previously in 4 of the cases, over seven years in 3 cases, over six years in 2 cases, over five years in one case and over three years in the case reviewed for the first time. The most recent case, operated on 13th January 1948, had gained 6 stones in weight and was free of symptoms.

All of the 10 cases previously reviewed were in good health with the increase in weight following operation well maintained. Since the previous review, however, 3 of the patients have developed occasional slight symptoms.

Mrs G, æt 51. Operation on 30th April 1945. This patient had suffered at intervals from dysphagia over a period of fifteen years and from severe dysphagia and frequent regurgitation of food after every meal during the previous year. She had remained perfectly well for five years after operation and was able to eat anything without any difficulty, and this is still the case except that during the last six months she has felt occasional discomfort after eating meat of any kind. Apart from this item of food, she can eat anything without discomfort and her weight has been maintained. At the X-ray examination on 27th June 1951 the barium was seen to pass through freely into the stomach. The œsophagus, however, did not empty completely and marked irregular peristalsis was noted and at the end of half an hour there was still a trace of barium in the œsophagus.

Mrs M, aet 51 The symptoms in this case had been present for one year before operation on 15th April 1946 Difficulty was felt with both fluids and solids and there was frequent regurgitation after meals The patient was free of all symptoms for a period of five years after the operation She still feels well and her weight is maintained Recently at intervals of five or six weeks she has had a sensation of wind in the epigastrium dispelled by a glass of warm water This sensation has been felt particularly when she has been worried At the X-ray examination on 26th May 1951 barium passed readily into the stomach There was still some dilatation of the oesophagus and the degree of peristalsis in the lower two-thirds was greater than normal Intermittent contractions came and went with great rapidity and were much more obvious during screening than in the films There was still a trace of barium in the oesophagus for half an hour but the patient had no discomfort

Mrs MacP, aet 75 This patient was seen first in 1927 when she was X-rayed by the late Dr Hope Fowler and a diagnosis was made of cardiospasm in an early stage She had been treated intermittently with the mercury bougie without much benefit An X-ray examination eight years ago showed that the oesophagus had become greatly dilated and peristalsis was very inactive A small diverticulum had formed a short distance above the diaphragm Six years ago she was sent from the north of Scotland by ambulance as an emergency case It was considered doubtful if she would stand the journey For some time she had been able to take very little nourishment She was dehydrated, fibrillating and very feeble Dr Gillies thought a general anaesthetic was out of the question I gave her a local anaesthetic with a view to gastrostomy Once before I had exposed the lower end of the oesophagus with local anaesthesia and had demonstrated a chronic peptic ulcer above the diaphragm by pulling down the oesophagus In this case also, after infiltrating the abdominal wall and the lesser omentum, I was able to expose the lower end of the oesophagus At this stage the patient was given a small dose of pentothal and the operation was completed within a few minutes The patient was able to swallow freely from the first and remained symptom-free till a few months ago Since then at rare intervals she has felt discomfort in swallowing solids such as meat or fish Her weight is maintained at 8 stones 10 lb as compared with 6 stones before the operation, and at the age of 75 she is still able to lead a normal and active life

All 3 patients were typical cases of cardiospasm and had been completely free of symptoms for over five years Each felt at intervals of a few weeks slight discomfort in swallowing solids such as meat All 3 patients were in good health and apart from these occasional lapses were able to take a full diet without any difficulty The remaining 8 cases were entirely relieved of their dysphagia None had to eat slowly and there had been no suggestion of regurgitation in any of the post-operative cases

The fact that slight symptoms had reappeared in 3 cases, after a long interval, emphasises the importance of determining the remote results in the evaluation of any method of treatment in this particular condition

X-ray Examination—Some evidence which may help to explain

the recurrence of symptoms is afforded by the X-ray examination of the cases in this series, particularly in regard to the size and emptying of the œsophagus after a barium meal

In contrast to the appearance before operation, there was a well-defined gas bubble in the fundus of the stomach. The absence of a gas bubble in cases of cardiospasm before operation is no doubt due to the large quantity of retained food and fluid in the gullet

There was invariably a rapid entry of barium into the stomach whether a thin or a thick medium was given. In all except in 2 of the cases in which the œsophagus had been greatly dilated there was a marked reduction in the calibre of the œsophagus which sometimes returned almost to a normal size

An almost constant abnormality present was the tendency of the barium to remain longer than usual in the œsophagus, sometimes for a few minutes or even for half an hour

When there is only a small amount of barium retained, the peristalsis may be almost normal, when the delay is more marked, irregular tertiary waves predominate and there may be some retrograde peristalsis (Fig 9)

The fact that there is some delay in emptying of the œsophagus after the dysphagia has been relieved is not appreciated by the patient, he differs in this respect from a normal individual with thick barium in the œsophagus who is conscious of its presence and gets rid of it by repeated acts of swallowing

The cause of the delay in emptying of the œsophagus is not apparent. It may be that there is still some trace of obstruction unrelieved by the operation, perhaps due to too limited division of the muscle or to scar tissue

An explanation worthy of consideration is that peristalsis in the œsophagus is abnormal in cardiospasm. Irregularities in peristalsis seen before operation suggest that the inco-ordination is not confined to the area of the sphincter. The same slight delay in emptying of the œsophagus was observed in my case of œsophago-gastrostomy soon after the operation, although barium was freely entering the stomach through an ample stoma. I have seen a different picture when the œsophago-gastrostomy has been done after resection of a malignant stricture at the cardia, in such a case, when the previously dilated œsophagus is otherwise normal, the barium may flow so rapidly into the stomach that it is difficult to visualise the œsophagus, although this can readily be done when the patient is recumbent and tilted so that the barium flows back into the œsophagus

The tendency of the dilatation of the œsophagus to persist in advanced cases of cardiospasm is in striking contrast to the restoration of the stomach to a normal size after a simple pyloric stenosis has been relieved by operation

In nearly all the descriptions in the literature regarding the results of the various operative procedures employed in cardiospasm, reference

is made to the fact that the radiological appearance of the œsophagus seldom shows an improvement corresponding to the relief of symptoms

The delay in emptying of the œsophagus and the irregular peristalsis present are sufficient to account for the discomfort or occasional slight difficulty in swallowing referred to in the cases with recurrent symptoms

Why these patients have symptoms is not apparent when it is recognised that some of the other cases with almost similar radiological findings are free of symptoms as these patients were till recently. One of the 3 patients with symptoms, a lady of 75, had had a greatly dilated œsophagus with minimal peristalsis for many years, and in her case the size of the œsophagus was little altered after the operation

CONCLUSIONS

From these observations it seems justified to conclude that Heller's operation, properly performed, offers a good prospect of relieving the symptoms due to cardiospasm

It should be preferred to other surgical measures when treatment by dilatation has failed. The immediate results of the operation are excellent, but in certain cases after a lapse of years there is a tendency for symptoms to return

Peristalsis in the œsophagus is abnormal in cases of cardiospasm, and even when the dysphagia has been completely relieved by operation and the œsophagus is reduced in calibre, there is frequently some delay in the final passage of barium into the stomach

The transpleural route is to be preferred if difficulty in exposing the œsophagus is anticipated from adhesions or from any other cause. The exposure for Heller's operation by the abdominal route is relatively easy in thin patients and this route should be selected when the patient is feeble and in specially poor condition

I am indebted to Mr I E W Gilmour and Dr John MacKenzie for the most recent review of my cases, and to Dr Rae Lyon for the detailed examination and report on five specimens of cardiospasm. I am also indebted to Professor R McWhurter and to Dr T M Prossor for their statements regarding the results of radiotherapy in carcinoma of the hypopharynx

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A REVIEW OF INFECTIOUS DISEASES DURING THE FIRST HALF OF THIS CENTURY

THE INCIDENCE OF INFECTIOUS DISEASES 1900-1950

By ALEXANDER JOE, M D , D P H , F R C P
Lecturer in Infectious Diseases, University of Edinburgh

IN presenting these reflections on the changes which have occurred in the common fevers over the first half of this century I have confined myself to these as they unfolded themselves in the Edinburgh City Hospital. For my information I have relied on the annual reports of my predecessors, C B Ker from 1900-24, W T Benson from 1925-36, and my own reports from 1937 onwards. As many of the cases coming into hospital were admitted for social and clinical reasons, for example a large number of our measles and whooping cough patients were sent in because of poor home conditions or because of severity of attack, the figures which I put before you are not to be regarded as exact vital statistics. Nevertheless they may be regarded as giving a fair picture of the ebb and flow of the principal communicable diseases in Edinburgh. I propose therefore to give a brief survey of these decades by decade.

The First Decade —The hospital report of 1901 records that typhus and smallpox were still to be encountered but were numerically on the wane, so that in 1901 there were 14 typhus cases with no deaths and 5 smallpox cases with 1 death. Typhus flickered on in twos and threes for a year or two but was never more to be a menace in Edinburgh although it lingered for some years longer in the sister burgh of Leith. Smallpox was only dormant for in 1904 a sharp epidemic comprising 170 cases with 15 deaths afflicted the city. However this was Edinburgh's last experience of variola on any large scale, and although limited outbreaks occurred in 1908 (20 cases with no deaths), 1920 (9 cases with no deaths) and 1942 (36 cases with 8 deaths), the disease has never assumed the severity that it had done in 1893-95 when there were 697 cases with 73 deaths. As a matter of fact in 1901, as judged by the numbers of patients brought into hospital, the principal infectious diseases were measles (626 cases with 9.5 per cent fatality), scarlet fever (601 cases with 3.3 per cent fatality), diphtheria (364 cases with 7.6 per cent fatality), whooping cough (174 cases with 25.8 per cent fatality), enteric fever (166 cases with 10.8 per cent fatality), and erysipelas (116 cases with 8.6 per cent fatality). As we shall see, with changing epidemiological and clinical fortunes, these, excepting enteric, were to remain the chief contributors to hospital admissions and the main preoccupation of those in medical charge for nearly the

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whole period under review Enteric has been mentioned as an exception and it was during this decade that it fell into the background, 93 cases with 5 deaths being recorded in 1906, and 30 cases with 3 deaths in 1911. A temporary alteration in the picture was provided in 1907 when Edinburgh had its first experience of cerebrospinal fever in epidemic form, 112 cases with 88 deaths being recorded in that year. What these must have cost the medical and nursing staff in effort and anxiety is revealed by the comment that treatment was drainage by lumbar puncture, hot baths, and various serums, the most effective being the hot baths. However, a supply of serum sent by Flexner of New York gave encouraging results in a limited number of cases.

The Second Decade—Unfortunately no annual reports were published during the first world war but from what statistics are available, and particularly those of 1911 and 1921, scarlet fever, diphtheria, measles, whooping cough, and erysipelas were as usual by far the greatest contributors to the hospital admissions. During the latter years of the first decade the increase in diphtheria admissions had been giving rise to some concern, and in 1911 there were 558 cases with a 7.5 per cent fatality. Ten years later, although the severity of attack as estimated by case fatality (6.6 per cent) had not increased, the total of 908 diphtheria admissions with 60 deaths was calculated to maintain that concern.

The Third decade—Although the hospital was well accustomed to admitting large numbers of cases of scarlet fever its resources were extended in 1921 as a result of a milk outbreak in Leith which brought the total annual admissions for that disease to 1983. It will give some idea of the sudden calls which may be made on a fever hospital when I mention that 529 of these patients were brought into hospital in one month (July). Apart from its prevalence some anxiety was caused in 1923, 1924 and 1925 lest the disease should be returning to the virulent type experienced in the seventies and eighties of the previous century, as the case fatality during these years remained relatively high at over 5 per cent. As a side-light on this severity I reported that in 1924, among 1604 cases of scarlet fever, nephritis occurred as a complication in 79, and of these 11 died, a nephritis case fatality of 13.9 per cent. However these fears were not realised although since the early twenties scarlet fever has continued to make by far the greatest contribution to our admissions. In the early twenties also there were the great recurring influenza epidemics and in 1922 influenza cases accounted for approximately one-tenth of the annual admissions, 450 cases with a 14.8 per cent case fatality. Although in succeeding years sharp outbreaks of influenza have occurred the hospital has never since been called upon to face emergencies on that scale. Also about this time a new disease appears in the records, epidemic encephalitis, but, although a most interesting condition, it never amounted to much numerically. The largest number of cases seen in any one year was 14 in 1923, and although the disease continued to appear sporadically in the wards up to 1930, by that time it had virtually gone. All through the decade

1920-30 the predominant diseases as usual were scarlet fever, diphtheria, measles, whooping cough and erysipelas, but towards the end of that period a newcomer thrust its way upwards in the list of the principal diseases in the shape of puerperal sepsis. This was not of course a new disease, a few cases had always found their way into the City Hospital annually, but admission to hospital began to be sought on an ever-widening scale as the result of the introduction of the puerperal pyrexia regulations. Thus we find that in 1931 there were 130 confirmed cases of this condition with an 11·5 per cent case fatality, and a relatively high admission rate of between 150 and 200 cases per annum was to continue to absorb the attention of the medical and nursing staffs till comparatively recent times. In the early twenties the change in type of infecting organism in enteric began to show itself. Up till that time typhoid infections were the rule, but in 1922 out of 15 cases 3 were paratyphoid B. Since then paratyphoid B infections have progressively increased until at the present time, among the few enterics encountered, it is most unusual to find a true typhoid. That enteric could not be regarded entirely as a disease of the past is shown by sharp outbreaks of 57 cases in 1927 and another of 71 cases in 1929, both of paratyphoid B fever. I have already drawn attention to the steadily mounting admissions for diphtheria throughout the second decade, and this persisted in the third decade so that in 1929 1135 cases, and in 1930 1086 cases were treated in hospital. In both these years the number of diphtheria cases narrowly exceeded those of scarlet fever but this was the high-water mark of the disease in recent times and never since have diphtheria admissions been anywhere near these figures.

The Fourth Decade—Again this period continued to be dominated by scarlet fever, diphtheria, measles, whooping cough, erysipelas and puerperal sepsis, scarlet fever and diphtheria being outstanding. Indeed in 1933 confirmed cases of scarlet fever treated in hospital reached the unprecedented figure of 3461, easily a record in the history of the hospital, and this was apparently due to an all-round epidemic prevalence during the year, and not to any particular incident such as a milk outbreak. Fortunately the high total of admissions was not accompanied by an increase in fatality and the percentage of fatal cases was well below 1 per cent for the whole of the decade and indeed was below 0·5 per cent in the latter half. Although after the high prevalence in 1929 and 1930 diphtheria continued to diminish on the whole towards the latter part of the decade, case fatality continued to remain high between 5 and 8 per cent for the various years. An interesting feature of the disease at this time was the diminution in the number of cases of the laryngeal type, whereas in 1930 and 1931 these had numbered 97 and 57 respectively, in 1938 and 1939 they had dwindled to only 17 and 7 cases. A comparative newcomer which appeared on the scene in the thirties was bacillary dysentery and confirmed cases mounted from 33 in 1933 to 101 in 1939. Cerebrospinal fever remained quiescent, never reaching more than 20 cases per

annum in the last half of the decade. One interesting feature of the epidemic situation was the appearance of poliomyelitis in any number, 21 cases in 1936 and 22 in 1938. Measles mortality showed a sharp fall to 0.73 per cent in 1939—it had moved between 5 and 10 per cent, for years previously—and from that time onwards the decline has been progressive. In 1939 there was a large drop in our total admissions owing to the dispersal of the juvenile population at the outbreak of war.

The Fifth Decade—This has probably been the most memorable in the history of the hospital. It began with heavy years in 1940 and 1941, all the common diseases contributing their quota, but outstanding being the epidemics of cerebrospinal fever with 317 cases in 1940 and 211 in 1941. The mitigating feature of these outbreaks, however, was that the case fatality had been brought down from approximately 70 per cent to well under 20 per cent, thanks to the sulphonamides. Looking at the period as a whole the most notable feature was the virtual disappearance of diphtheria. The number of cases fluctuated between 671 in 1940 and 387 in 1945, but thereafter a well marked decline set in and the figures are worth giving in detail—1946, 188 cases with case fatality of 6.38 per cent, 1947, 51 cases with 1.96 per cent case fatality, 1948, 18 cases with 5.55 per cent case fatality, 1949, 7 cases with no deaths, and in 1950, 2 cases with no deaths. In parenthesis it may be said that so far in 1951 we have not seen a single case. Scarlet fever behaved in rather an extraordinary way also in this period, falling from 1535 admissions in 1942 to 238 in 1947. This last was the lowest number of scarlet fever admissions ever recorded at the City Hospital, but a sharp uprise has occurred since then and in 1950 we were over the 1000 mark once more. It should be mentioned also that in the five years 1946-50 inclusive there has not been a single scarlet fever death. The decline in the measles mortality noted as setting in in the fourth decade has persisted, and in 1950 among 269 cases there was not a single death. As regards the other killing diseases there has been a marked drop in the admissions of puerperal sepsis, so that in 1949 and 1950 only 26 and 9 cases respectively came into hospital and there were no deaths. Erysipelas cases have also much diminished and there have been no deaths among a total of 81 cases admitted in 1949 and 1950. Whooping cough still presents a challenge, however, and while the case fatalities ranging from 10 to 20 per cent or over prevailing up till the early forties are no longer experienced, it is a good year even now when the proportion of deaths is under 5 per cent. Apart from the decline in morbidity and mortality witnessed in the diseases mentioned one important event in the decade was the smallpox outbreak of 1942, which left a lasting impression on all who had anything to do with it. Then we had the poliomyelitis outbreak of 1947 with 173 cases and a 12 per cent fatality which was our share of the first really widespread epidemic in this country. Although relatively quiescent in 1948 and 1949 the disease flared up again in 1950 so that we had 89 cases admitted to hospital. The rise in admissions of bacillary dysentery to 597 and 482 in 1944 and 1945 was also of some

interest although from the standpoint of severity and case fatality these infections have never been an urgent problem. Finally, since 1948 we have devoted a good deal of attention to infantile gastroenteritis and well over 100 cases per annum are now admitted. Our fatality in 1948 was the discouraging one of 17 per cent, but we have done somewhat better in 1950 with a case fatality of 3.17 per cent in 126 cases.

From this brief outline it will be apparent that scarlet fever, diphtheria, measles, whooping cough, and erysipelas were our main preoccupation over the greater part of the first half century. Sharp outbreaks of such diseases as enteric and cerebrospinal fever occasionally obtruded themselves, but it was only from the late twenties onwards that new problems appeared on any scale in the shape of bacillary dysentery, puerperal sepsis, poliomyelitis, and infantile gastroenteritis. Puerperal sepsis and gastroenteritis were not of course new diseases, and it was as a result of administrative action rather than epidemiological change that these diseases became important in fever hospital practice. Quantitatively therefore, until the latter half of the fifth decade, apart from the great decline in enteric which had taken place in the first decade, there was not a great deal of change except the change in character that individual epidemic diseases assume from time to time, *e.g.* a particularly high incidence of a severe form of nephritis as a complication of scarlet fever has been mentioned as occurring in 1924, or again, over a limited period, an undue proportion of cases of one or other of the exanthemata will exhibit aberrant rashes which in themselves will run true to type and manifest a curious atypical sameness. These cyclic changes in clinical character and severity are characteristic of epidemic disease. In the latter half of the fifth decade of course quantitatively the changes have been remarkable, particularly in respect of the disappearance of diphtheria, the fall almost to vanishing point of puerperal sepsis, and the rise of poliomyelitis.

Even with full recognition of these quantitative changes it is in the qualitative aspects of the common fevers that the most impressive alterations have occurred, and in none have these been better exemplified than in scarlet fever. Right through the first half of this century there has been a progressive diminution in severity of scarlet fever, and it is important to note that this decline was operating well before the introduction of the potent remedies which have emerged in the last few years. As evidence of the decline in severity we can look to the disappearance of the malignant or toxic, and the septic or anginose forms of the disease. For example, in 1924 in a total of 1604 cases there were 19 of the toxic variety with 16 deaths, and 34 of the septic variety with 16 deaths, but over the next few years first the toxic and then the septic type disappeared and from 1930 onwards the disease was seen only in the simplex form. It should not be assumed, however, from its nomenclature that the simplex type was without its problems, since complications even in this form of the disease were frequent and relatively constant in incidence, and that they were serious can be appreciated from the fact that in the years 1933-36 inclusive 113

mastoidectomies were performed among 7276 patients suffering from scarlet fever. At the present time, no doubt owing to the introduction of penicillin, the necessity for performing this operation has practically disappeared. Other common complications such as acute otitis media, adenitis, rhinitis, arthritis, and nephritis have also almost reached vanishing point, and it is quite an occasion in my fever class when I can show any one of these. Perhaps with reference to the decline in the complications of scarlet fever one reservation ought to be made, and that is in respect of endocarditis. Although never very common, at least during the period while the patient was under observation in hospital, this has not declined, and indeed in some years appears to have been on the increase. With this possible exception it is clear that both epidemiological change and therapeutic advance have combined to deprive scarlet fever of its severity. Whether this epidemiological change will be permanent is a question that no experienced epidemiologist will be likely to answer hastily. All we do know is that scarlet fever provides the classical example of change of epidemic type which has altered certainly twice and probably three times within the limits of modern history.

In diphtheria, with one important exception, there was little evidence of change of clinical type, and case fatality rates, though variable, remained over and sometimes well over, 5 per cent right up to 1942. The hæmorrhagic type had probably become less common, but the most striking change observed by those with much experience of the disease was the decline in incidence of the laryngeal form of the disease. For example in 1903 Claude Ker noted that 50 per cent of the diphtheria deaths were due to laryngeal diphtheria. By 1924 it accounted for 28 per cent, and in his annual report for 1935 Benson found occasion to comment on the virtual disappearance of laryngeal diphtheria. However, this form of the disease, although much reduced, never entirely ceased to trouble us until the disease itself vanished. Another feature of diphtheria in the first half of the century was the progressive shift in the incidence of diphtheria mortality from the pre-school to the school age. This was not due to an alteration in the incidence of the disease but was the result of a proportionately smaller decline of the fatality in the 5-9 than in the 0-4 years age group. I agree with those who attribute this alteration mainly to diminution in the average size of the family, and, if we accept this, we see how apparently unrelated social phenomena may initiate epidemiological change. Perhaps at this point I may suggest that it is possible some very interesting epidemiological changes may occur as a result of the mass immunisation of the child population as there is some evidence that adult immunity, brought about in the past by sub-clinical infection, is on the wane. If this is substantiated then we may expect diphtheria, should it be introduced, to become predominantly a disease of adults.

With regard to measles I could not say with confidence that there has been much alteration in its clinical manifestations, or its complications, during the past thirty years, although we all know that the

measles mortality has been steadily on the decline and that this has been definitely accelerated since the late thirties. Since measles mortality was a pneumonia mortality to a great extent, I have no doubt in my own mind that this acceleration was in large measure due to the introduction of the sulphonamides. Apart from mortality, measles has always been important on account of the chronic morbidity which often followed an attack. Chronic otorrhœa for instance had become a serious public health problem and much of this could be attributed to measles in childhood. Similarly with regard to visual defects, and, though Marshall and Seiler in 1942 reported that the specific fevers were a comparatively unimportant cause of blindness, of the small number of cases discovered in their survey three-quarters were due to measles. Since penicillin became available eye and ear complications of measles have practically disappeared from our wards, and consequently as a source of chronic morbidity the disease should cease to be important. Since the early twenties when interest in post-infective encephalitis was aroused by the investigations which pointed to post-vaccinal encephalitis as a direct sequel of vaccination, much has been written about its occurrence in measles, in which it is probably more frequently found than in the other common fevers. Fortunately rare, this complication is a good example of what I have referred to as cyclical change in the characteristics of individual epidemic diseases, as it appears in some epidemics with greater relative frequency than others.

Serious though whooping cough remains, and, from the point of view of treatment, still an unsolved problem, it is definitely on the wane as a killing disease, and the high hospital case fatalities of over 10 and even 20 per cent are no longer experienced. In fact, although fortunately we have seen little of it in Scotland in modern times, the only disease which appears to have retained its capacity to reproduce its malignant type is variola major. Observing the comparatively small number of cases which appeared in Edinburgh in 1942 we seemed to be translated to the clinical atmosphere of earlier days, confronted as we were by a disease which assumed a malignant form in about a quarter of the cases, and which evolved relentlessly to its fatal and loathsome conclusion without the slightest prospect of alleviation. It is true that in the cerebrospinal fever epidemics of 1940 and 1941 the fulminating type was also relatively common but here we were not entirely helpless as even in this type sulphonamide treatment was not without its successes.

As to the factors governing these qualitative changes in the common fevers these are undoubtedly complex, and discussions on their nature, and views as to whether they will continue to operate, would require a whole evening to themselves. Our recent experience of poliomyelitis should teach us to be wary, and, while modern triumphs in prophylaxis and treatment of the acute infectious diseases may give us much cause for satisfaction, we should never forget that only the longest of long term views are permissible in epidemiology.

A REVIEW OF INFECTIOUS DISEASES DURING THE FIRST HALF OF THIS CENTURY

CHANGING CONCEPTS IN THE COMMON FEVERS

By THOMAS ANDERSON, M D, F R C P E, F R F P S G

Reader in Infectious Diseases, University of Glasgow

I HAVE thought that the purpose of this symposium might be best served if, instead of remaining completely factual in my outlook, I were to try to present to you a more philosophical background as it were, to attempt to portray the background upon which our modern view of infectious diseases is based. My remarks may be conveniently divided under two headings—first, what might be called changes in the general principles underlying our attitude to infectious diseases, and, second, changes which have an important application in treatment of the patient in hospital or in the home.

GENERAL PRINCIPLES OF THE BEHAVIOUR OF INFECTIOUS DISEASES

(a) *The Place of the Infectious Diseases Hospital in the Community*—There is little doubt that when the fever hospitals were first opened their sole purpose was regarded as preventive. The principle was accepted that the isolation of infected persons in the infectious diseases hospital would remove from the community the source of infection and, in this way, eradicate the common fevers. Although for a long time it has been appreciated that this cannot be carried out effectively, it is true to say that there remains a conception that the fever hospital's main purpose is the isolation of infected persons with a view to the saving of the remainder of the community. Now there may have been something to say for such a view when the prevalent diseases were due mainly to dirt—typhus, typhoid and cholera, for example—but the vast improvement in civic hygiene which marked the end of the nineteenth century and the beginning of the present century itself caused a reduction in infectious diseases of this type. During the present century more and more attention has had to be paid to the respiratory tract infections for the great majority of the common fevers of to-day are spread by the air. Now, whereas the sterilisation of water and the separation of water from sewage, both of which measures so greatly reduced the prevalence of the bowel diseases, may be regarded as comparatively simple matters, the sterilisation of the air presents a much more serious problem. When it is appreciated that many of the

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respiratory tract infections are caused by organisms commonly present in the throats of healthy individuals, and when we realise that much of the time of any individual in the adult community is now spent in what might be termed crowds, either in travelling to or from his work, or while at his work (with a constant, consequent transference of organisms from one person to another), it becomes obvious that the number of infected persons outside of the fever hospital greatly exceeds that in it. Now I can almost hear you say "Surely you are not advocating a policy that the infectious diseases do not require to be admitted to hospital at all." It is important in this respect to make a distinction between what might be called "endemic" and "exotic" infections. The endemic infection which is constantly present in the community frequently gives rise to minimal attacks so that there is a wide variation in the severity of infectious disease which results—much of it escaping recognition. The "exotic" infection, on the other hand, which is rarely present in the community tends to produce a much more obvious form of the disease, so that practically all the cases are readily diagnosed and admitted to hospital. Since very few members of the community have had experience of these exotic infections it is a matter of public health importance to achieve early diagnosis and early segregation in the fever hospital, for then the foci of infection are greatly reduced in number. The fever hospital, therefore, like any other specialist hospital exists nowadays mainly as a place in which expert medical and nursing attention may be given to severe forms of acute infective disease and only to a small extent as an isolation unit for unusual epidemics. For many of the common infections it would be a waste of hospital beds to suggest that all cases be removed to hospital, and most public health departments now carry out a policy which ensures that patients receive hospital care either by reason of the severity of their illness or because social conditions make it imperative that the patient should receive more adequate attention. Fortunately, it is true to say that the treatment of most infectious diseases can be adequately carried out in the home provided a few simple precautions are taken.

(b) *Infectious Diseases as a Problem in Biology*—For long into the present century there is little doubt that almost the sole emphasis in infectious diseases was placed on the pathogen. No doubt this was largely motivated by the early work done by the bacteriologists in ascribing to certain diseases certain parasites. As a result, we regarded certain infectious diseases as being "caused" by certain organisms, the underlying implication being that all the clinical manifestations of infection were produced by the organism. In recent years we have tended to move away from this concept and to emphasise more and more that the host plays a large part in deciding the pattern of the infectious disease. This question of host-parasite relationship is undoubtedly a very important one and it may be conveniently dealt with under three broad groupings: first, on the mass scale,

second, on the individual scale, and third, on the cellular scale. So far as the mass scale or the community is concerned there is no doubt that the behaviour of the community imposes itself upon the pattern of infectious diseases prevalent in the community. Two examples may suffice to make my point. Up to the beginning of the recent war, one of the important claims made by the hygienist was that the improvement in public sanitation and in personal hygiene had resulted in the virtual disappearance of the bowel diseases from this country—dysentery was uncommon and typhoid only reared its head on occasions with small epidemics. During the last eight or ten years, however, dysentery and food poisoning have become almost the most common infections prevalent in the British Isles. What has occasioned this change? Is it the appearance of new organisms? Is it the development by old organisms of new capacities to attack the human host? It seems very unlikely that the explanation lies in anything to do with the parasite. It seems much more probable that the occurrence of strict rationing at the beginning of the war which resulted in the opening up of new restaurants often in premises quite inadequate for such purposes—the encouragement given to school canteens and work canteens to supply mid-day meals—the shortage of foods which resorted in the reheating of leftovers, and the development of the transport industry with its mass of men moving about the country from one place to another and eating in small unhygienic restaurants in small villages—all of these combined to change the community from one where all fed at home to one where everyone was taking some meals outside. It seems likely that this change has exposed man to risks entirely novel to him. Far from the organisms having increased in virulence or in attacking power, it is probably true to say that the very mildness of the illness produced by most of them is itself important in that it encourages the individual to remain at work when he is suffering from the disease with the result that any fault in hygiene results in a greatly increased spread of infection. Or, to take another example, the so-called gastro-enteritis of infancy—there is no doubt that this disease was very prevalent at the beginning of the century. Recurring epidemics, usually in the summer time, took a large toll of child life. Then in the 1925 period with the disappearance of horse traffic and its replacement by motor traffic, the disease almost disappeared. There can be little doubt that the high prevalence of this infection in the early 1900s was largely due to contamination by flies. Then, in the late 1930s, the disease reared its head again. This sudden reappearance was not always associated with summer epidemics. On some occasions the outbreak occurred during the winter. Association with flies could rarely be proved. Indeed, the careful examination of these cases often failed to reveal any evidence of infection and pathogenic organisms could not be isolated from the stool. The one feature which was common to nearly all epidemics, however, was that breast-fed babies usually escaped, whereas bottle-fed babies were much more susceptible.

to attack. Much work yet remains to be done on this condition but, in my view, the ultimate cause lies in some fault of nutrition which results from bottle feeding so that resistance to all types of infection is reduced. These two examples will suffice, although others could be given to indicate that the pattern of infectious diseases prevalent in any community is not merely decided by the kind of prevalent organisms but by the behaviour of the hosts in a community.

When we come to the individual the same general principle may be applied. All hosts are not the same in their make-up. There is great inequality in their capacity to resist infection. As a result, all types of clinical manifestation may be recognised when the infectious disease is prevalent in the community. Epidemics due to the meningococcus form an excellent example of the variation in response to the same pathogen by different hosts. Our modern view of a meningococcal epidemic would be that by far the great majority of the populace become mere carriers of the organism, either for short or long periods. There is, it might be postulated, a naso-pharyngeal barrier to the passage of the organism into the tissues of the host so that the epidemic is, as it were, an epidemic of carriers. In a few individuals whose resistance has been lowered (and it is probably some precedent lowering of the cellular state of resistance of the nasopharynx that is responsible) the organism, having penetrated the nasopharynx, enters the bloodstream and rapidly penetrates the blood brain barrier to produce meningitis. In the great majority of these cases the organism merely stays in the bloodstream for a very short period and produces little or no damage during transit. But, in a very small number of persons, the entry of the meningococcus into the bloodstream is followed by the most widespread damage and an acute fulminating septicæmia results—an illness which may kill the patient in a matter of a few hours. Here again we see that it is not any undue virulence on the part of the organism which causes this variety in the clinical pattern of disease, but the interplay between parasite and host which produces in one person a carrier state, in another meningitis, and in another a virulent septicæmia.

But the picture of host-parasite relationship must eventually be taken down to the smallest scale, namely, to the cell and here one must understand the difference between the bacterium and the virus as a cause of infection. One of the profound differences between them is that the former is an extracellular parasite existing in the intercellular spaces, whereas the latter is an intracellular parasite, breeding inside the walls of the cell itself. Now although this point is appreciated by most clinicians, few have taken it to its ultimate interpretation. So long as the attacking parasite remains outside of the cell, it is obvious that treatment will be a comparatively simple matter. Any substance which enters the bloodstream and passes from the blood vessel into the tissue fluids will reach the organism and, with our modern forms of chemotherapy, may be expected to subject it. Virus infections, on the

other hand, present an entirely different problem. Here, when there is clinical manifestation of disease it may be accepted that the virus is already inside the cells. As a consequence, two conclusions are reasonable. First, any therapy which is going to kill the virus must almost certainly kill the cell as well, and secondly, virus damage will, as a rule, result in cellular damage and, in some tissues the replacement of important cells destroyed by virus may be impossible. The introduction of powerful chemotherapeutic agents has induced the concept in our minds that all infectious disease will ultimately prove amenable to treatment, but it needs to be emphasised that the diseases which so far have proved susceptible to chemotherapy are practically all bacterial diseases. The only near-virus diseases which we have been able to treat are the typhus group of fevers, where the rickettsiæ not only exist intracellularly but also show periods of invasion of the bloodstream. I think it is true to say that there is no real evidence that true virus infections of a systemic character have yet proved susceptible to chemotherapy.

(c) *The Importance of Social Conditions*—All of the early epidemiologists laid great stress on the environmental background of the infectious diseases. There can be no doubt of the importance of social conditions in the spread of infectious diseases. But two aspects of social conditions which have not perhaps been given the emphasis that they should have received are nutrition and family size. My experience would suggest that the most striking change that has occurred in the last twenty years is in the nutrition of children admitted to hospital. The greatly increased neonatal and child welfare supervision, the supply of milk to schools and school meals, all of these have played an important part in increasing the resistance of the host to bacterial infection and have an important bearing on the reduction in the severity of infectious diseases. We are often misguided enough to believe that the reduction in severity is entirely due to chemotherapy and we need to be reminded that the infectious diseases had been improving in this respect, long before chemotherapy was introduced. An analysis of the figures in Glasgow shows that mortality from pneumonia for example had fallen greatly in the ten years 1920-1930. The freedom of the population from serious infectious disease during the war was probably due to the wise feeding policy that was adopted. Nevertheless, improved nutrition and the rapid subjection of bacterial infection produced by modern chemotherapy may carry certain dangers. The importance of realising the difference between bacterial and virus attack has been emphasised. Although it is reasonable to argue that a well nourished host may be the better able to withstand bacterial attack it might also be argued that if the virus is dependent upon the nutritional metabolism of the cell then it may be that a cell which is actively metabolic and well nourished is preferred by the virus. Such a concept is not an entirely novel one. We have long known that the rash of smallpox, for example, prefers the exposed parts of the body. We say that the rash appears

A REVIEW OF INFECTIOUS DISEASES

on the traumatized skin Is it not possible the virus prefers these sites because the cells are there very active and in continual replacement As a more recent example poliomyelitis might be cited It might be suggested that the increased prevalence of poliomyelitis in the last few years may be due to the enhanced nutrition of the cells of the body which encourages the invasion of the poliomyelitis virus But if this seems rather a tenuous argument to put forward, there can be little doubt that the virus prefers central nervous system cells which are in a state of activity, and Ritchie Russell has shown that excessive muscular activity may play an important role in initiating severe paralysis It is easy to think of this as indicating that a tired muscle is more likely to become paralysed but it seems possible that the virus parasitizes a cell which is in a state of great activity and therefore able to produce the kind of feeding material which the virus prefers

In regard to the size of family little work has been done in trying to correlate the reduction in severity of infectious diseases with the reduction in the size of family But it may be that one of the important factors which has reduced the severity of such conditions as measles in the last twenty years is smallness of the modern family With a large family the presence of measles in the household (introduced so often from school) resulted in the infection of a considerable number of younger siblings Nowadays, it is not uncommon to find that the older member of the family has passed through the common infectious diseases before the newcomer arrives This has the effect of raising the age of attack and, as a result, the severity of the illness is reduced

CHANGES IN THE MANAGEMENT OF THE DISEASES

(a) *The Importance of Cross-Infection*—It may come as a surprise that I would regard our increased knowledge of the means of cross infection as perhaps the most important advance in knowledge that has taken place in recent years At the beginning of the century and well into the 1920s the concept was generally held that infectious diseases were spread by droplet infection It is true that in the case of smallpox and chickenpox some attention was paid to what was termed aerial transfer but the mode whereby aerial transfer took place was not at all clear Mainly as a result of the work undertaken by Cruickshank in Glasgow and by the Wells in the United States of America it soon became apparent in the 1930s that infection could be spread by a variety of means—principally, by the air and by the dust It was appreciated that the moist droplets, in their descent through the air, became reduced in size by drying and that by these much smaller “droplet nuclei” infectious material could remain suspended in the air to be carried by draughts considerable distances, or might settle on bedclothes or on the dust of the floor to be raised during bedmaking and the domestic sweeping Had it not been for the war this would

have had a profound effect upon fever hospital design, for it is obvious that to congregate infectious diseases in large numbers in open wards, as was the practice in the past, enhances the risk of cross-infection. Ward units in fever hospitals should be small and not contain more than four to six persons. Further the method of nursing should demand greater attention to personal hygiene so that the transference of infected material from patient to patient is reduced to the minimum. One might indeed go so far as to say that the occurrence of certain complications forms an excellent index of the efficiency of the management of a hospital for infectious diseases. Thus, otitis media is recognised as a complication of scarlet fever, but there is no doubt that a considerable proportion of such cases develop this complication not as a result of the original infection but because the patient acquires another organism from his neighbours when he is convalescing from the original attack. It is thus possible to say that if an otitis media develops in the first week of scarlet fever it is likely to be a complication of the original infection, but that when it occurs thereafter it is much more likely to be due to cross-infection from some other member in the ward. Such a view is of great importance for it follows that if the cases are properly managed the incidence of the complication may be reduced very considerably. Dr W. T. Benson enunciated the view that when a measles ward received more than a quarter of its complement with a broncho-pneumonia present on admission, then cases admitted to that ward without broncho-pneumonia were very liable to contract it. This knowledge of cross-infection is of the very greatest importance in children's wards in no matter what type of hospital and the necessity to take strong measures to avoid cross-infection in burns and plastic surgery units has, of course, already been widely appreciated.

(b) *Chemotherapy*—Little need be said about the progress of chemotherapy in the last fifteen years. Most of us will agree that our change in outlook in regard to treatment has been profound. During the period 1900-1935 the accepted view was that the correct treatment of an infectious disease involved first, finding its cause, and then second, producing an antiserum in some larger animal. However, apart from diphtheria, scarlet fever and tetanus, the use of antitoxins and antisera have now little place in treatment. Nevertheless, as we progress from one antibiotic to another, it is perhaps worth recalling the great advance which was made with the introduction of sulphonamides in 1935. It might not be too much of an exaggeration to say that the sulphonamides played a more important role than penicillin in the recent war. The vast epidemic of meningococcal infections which marked the outbreak of the war would have had a disastrous effect on life—and on morale—if we had not possessed an effective form of therapy which reduced the mortality to between 10 and 15 per cent. The widespread prevalence of dysentery in the Middle East during 1942 was effectively controlled by sulphonamide and the part played

by these chemicals in restoring troops to the field more rapidly was immense

But the story has advanced greatly since those earlier days. We now have a chemotherapeutic material capable of attacking almost every bacterial disease. When one method fails, another can step forward to take its place. Whooping cough alone remains amongst the infectious diseases as still resistant to chemotherapy. The list of the victories is a most impressive one, the sulphonamides with their great activity against meningococcus infections, pneumonia, urinary infections and the dysentery group, penicillin effective against staphylococcal, and pneumococcal infections, streptomycin and its efficacy in some forms of tuberculosis and finally, chloramphenicol and aureomycin with their wider range of activity bringing enteric fever and typhus under control.

(c) *Secondary Effects of Chemotherapy* —The materials are now in our possession which profoundly affect bacterial life. If bacteria were only to be found in the human body during infection then of course to kill them would always be a good thing. But we all carry in our nose, throat and bowel a microflora which, it would not be too fanciful to suggest, is of the greatest importance for our health. Now the administration of chloramphenicol to a patient means in effect that we sterilise his nose and throat in a matter of six to twenty-four hours and kill a high proportion of the organisms in his intestinal tract in a matter of two to three days. Such a change is an unnatural one and since nature seems to dislike a vacuum it is not an unnatural effect of this change that other bacteria should enter to take the place of those that have left. Under such treatment the predominant faecal flora may become fungal. Thus, although fungi can be grown infrequently from the faeces of pneumonia patients on admission to hospital, they are an almost invariable finding after four or five days' treatment with an antibiotic of the nature of terramycin. In many cases the sputum produces a considerable growth of monilia. In this country where these antibiotics are still on short supply and are very expensive such changes produced have not been great in magnitude, but in America the changes in the flora of the throat have already become considerable and deaths from monilia infection have actually occurred. I would be so bold as to prophesy that the increasing and widespread use of these powerful antibiotic agents may produce profound changes in the host and that this will, in time, show itself in a changing pattern of infectious diseases.

It is perhaps of interest to draw your attention to another aspect of biological relationships. You will recall that during the war the introduction of D D T was heralded as a major advance. The application of D D T to the prevention of typhus fever made a great contribution to the Italian campaign. And yet to-day, within ten years of the introduction of D D T, we find that flies are developing resistance to it and that in certain regions the prevalent form of fly is now completely

resistant to the action of D D T Further, and of very great interest, it has been found that individuals in towns who have had no known contact with D D T whatsoever yet may show the presence of D D T in their blood, presumably resulting from the ingestion of fruits and other materials which have been sprayed with D D T Our duty as doctors seems clear—we must attempt to prevent and, when not preventable, to treat successfully all acute infections It is well that we should constantly remind ourselves that in so doing we are interfering with a biological relationship Such interference cannot be undertaken lightly Bacteria and viruses, like the poor, will be ever with us When the host-parasite relationship is simple (as in the case of diphtheria) a very simple mechanism may induce complete immunity in the host But where, as in the majority of infections, the host-parasite relationship is complicated then we are unlikely to interfere with impunity The parasites will tend, in time, to find a method of circumventing our form of interference The newest antibiotics place in our hands the means of making profound changes in the microbiology of man Let us see that we use them with thoughtfulness

DISCUSSION

Colonel Morison, opening the discussion, recalled that in 1905 he was in charge of fever wards in a London Hospital and on his return from India in 1920, he was shown over them by his old chief, who reminded him that, while in 1905 toxic scarlet fevers were very common, they were rarely seen now

Another point he was interested in was Dr Anderson's reference to the fall of infantile enteritis after 1910 being due to the disappearance of horses Colonel Morison thought that in London it was much more likely to have been caused by the chlorination of the water supply introduced by Sir Alexander Houston He had noticed this occurring in India

Dr Douglas Robertson thought that scarlet fever was the outstanding instance of a disease which had varied in intensity from time to time Eighty years ago it was a dangerous killing disease, whereas now it was almost trivial We had no convincing theory to account for this variation in severity He considered it anomalous that a case of streptococcal tonsillitis with a rash should be isolated in hospital, while an equally infectious case without a rash was kept at home

Although whooping cough was regarded as one of the most fatal diseases in children under five, this had not been his experience Possibly he had been fortunate

Dr Robertson was disappointed that the most deadly of all infectious diseases in this country had not been mentioned—tuberculosis Patients with scarlet fever were rushed off to hospital, while young children were still allowed to remain in close contact with tuberculosis under shocking housing conditions It was a tragedy that we were still seeing cases of tuberculous meningitis almost certainly due to direct infection from near relatives in the home It was our duty, as medical men and women to do all we could to arouse the conscience of the nation and of our health and housing authorities to look

upon tuberculosis as the gravest public-health problem facing us to-day, and to take decisive action with a sense of urgency

Dr A Fergus Hewat said that he had had a good deal to do with cerebro-spinal fever during the 1914-18 war, and had been struck by the wonderful recovery rate resulting from serum intrathecal injections

Dr Hewat had at one time been in charge of a boys' school for a year and had to look into the subject of fevers at that time. He had been particularly interested in the introduction in Dr Claude Ker's book on Fevers published in 1909 to the subject of smallpox, which ran as follows — "It is a subject for legitimate regret that a textbook on fevers, written a century after the introduction of vaccination, should still have to include an account of a disease which should long ago have been classed with such conditions as the 'Sweating Sickness,' or the 'Black Death,' and relegated rather to historical treatises. It is an interesting and curious comment on our boasted civilization that, with the means of absolutely preventing smallpox at our disposal, we allow the prejudices of a small minority to still expose the country to not infrequent outbreaks of a peculiarly repulsive and filthy disease. But unfortunately, so long as vaccination and re-vaccination cannot be universally enforced, smallpox will continue to be with us, and, unfortunately also, will continue to be the cause of most regrettable loss of life and waste of money."

Also quoting from the same book (p. 183) there was an interesting paragraph on the value of vaccination — "The admirable results obtained by systematic *re-vaccination* are perhaps the most striking proof of the protection which can be secured if full advantage is taken of Jenner's discovery. In Germany, since re-vaccination has been enforced, smallpox has been almost unknown. The few individuals who contract it are for the most part foreigners who have not been re-vaccinated." "Contrast Berlin, with its 12 beds for smallpox in a pavilion of a general hospital, with London, with its 2500 beds in hospitals specially constructed and maintained for smallpox alone. The German law insists on re-vaccination at school age and the male adult population is again re-vaccinated on entering the Army." Dr Hewat asked what was the present position in regard to smallpox.

Dr Hewat expressed the cordial thanks of the meeting to the two speakers for their most interesting and instructive papers.

Dr Joe, in reply, said he had not much to add, but he too had received great stimulus from Dr Anderson's paper.

With regard to the chlorination of water, Dr Joe drew attention to the fact that the Edinburgh water supply was not chlorinated until the outbreak of war in 1939 but hospital admissions for bacillary dysentery continued to rise until 1944 and 1945.

Scarlet fever, Dr Joe pointed out in reply to Dr Robertson, is not merely streptococcal tonsillitis with a rash. The rash is not unimportant as it is the expression of a specific generalised toxæmia, which, in the malignant form of the disease, can kill the patient.

Tuberculosis had not been touched on as he had understood his remarks were to be confined to the acute fevers. However, as far as hospital treatment was concerned, lack of nursing staff was largely at the root of the trouble and failure to recruit nurses was due to fear of infection. Until this difficulty could

be overcome and defective provision of housing remedied the disease would remain a problem

Dr Anderson, replying, said he was interested to hear Dr Brownlee's name mentioned—his laboratory at Ruchill was called the Brownlee Laboratory

Dr Anderson regretted the omission of tuberculosis but he understood that "The Common Fevers" was the subject under discussion. He agreed heartily with Dr Robertson's remarks. During the summer he had arranged a conference in Copenhagen and had been impressed once again by the Danish attitude to tuberculosis. One never saw a case of tuberculous meningitis in children. He quoted the case of Dr H. C. A. Lassen who started with 100 beds set aside for the treatment of children with tuberculous. Since 1935 the numbers had gradually fallen until he had only 14 beds occupied. Until this country became as conscious of the disease as the Danish medical profession and general public, we could hope for little improvement.

HÆMATEMESIS AND MELÆNA

By D M F BATTY, M B, F R C P Edin

Assistant Physician, The Royal Infirmary, Physician, The Deaconess
Hospital, Edinburgh

INTRODUCTION

IN opening the discussion on hæmatemesis and melæna, I at once feel envious of Mr Samuel Pickwick His observations on Tittlebats and the Source of the Hampstead Ponds so unfortunately omitted from the text of the *Posthumous Papers*, must have struck an original note even when delivered before the famous Club he founded In sharp contrast, our Society meets to discuss a condition upon which each member, well informed and wise by the teaching of slow experience, can express opinion and find himself in general agreement upon principle and in dispute only on matter of detail Not assembled to register some massive development in medical science, we are met to record the changed state of mind that now stands revealed in us who have held in our hands the unpredictable fortunes of our fellow-men suffering from hæmorrhage high in the alimentary tract It is a sobering fact that in spite of our new thoughts and methods, barely five more lives are now saved in every 100 cases when comparison is made with the older statistics

Our purpose is well served if the term hæmatemesis is confined to the vomiting of blood in moderate or greater amount, and melæna to the passage of black, tarry stools

CASE MATERIAL

The anatomy and pathological background of this condition is well illustrated by reference to the records obtained by autopsy upon 145 cases who succumbed to hæmatemesis and melæna in Edinburgh Royal Infirmary during the years 1940-49 Although a slight increase in numbers can be discerned during the last five years of this period, merry War and disgruntled Peace have each failed to make significant change in the autopsy rate for this disorder in Edinburgh, a city so remarkably free from the anxieties of aerial attack Figures culled from such a source fail to give accurate impression of a disability from which most patients recover Study has therefore been additionally made of the clinical records of 145 patients suffering from hæmatemesis or melæna who have come under personal observation during the last five years The diagnosis in this series is based upon the clinical manifestations, aided by biochemical and radiographic evidence, supported in some

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2nd May 1951

cases by gastroscopy and in other instances by operation or ultimate autopsy (Table I)

In common with other published tables, the figures in each series fail to give satisfaction. Listing only a disease process causing hæmorrhage, the table is not only inadequate, for mention is not made of other disease contributing to the hæmorrhage or ultimate issue, but also inaccurate for detail is lacking of the multiple ulceration commonly found in the gastro-duodenal area. For example, one patient with hepatic cirrhosis died of hæmorrhage caused by a large gastric ulcer penetrating varices extending from the œsophagus to the lesser curvature. A further case who survived operative repair of a perforated anterior wall duodenal ulcer succumbed within a few days to severe hæmatemesis and peritonitis. Of 7 other ulcers demonstrated in the gastro-duodenal area at autopsy, 2 had been the seat of hæmorrhage and 2 of recent perforation, each of these catastrophes affecting ulcers in the stomach and in the duodenum.

TABLE I

Diseases	Autopsies (1940-1949)	Ward Cases (1946-1950)
Hæmatemesis and/or melæna	145 (of 5409 cases)	145
Melæna neonatorum		1
Foreign body in œsophagus		1
Cirrhosis of the liver	16 (of 84 cases)	1
Portal vein tumour	1	
Œsophageal hiatus hernia— with gastric ulcer	1	
with duodenal ulcer		1
Peptic ulcer— of œsophagus		2
of stomach	50	28
of duodenum	55	67
Anastomotic	3	5
Acute erosive gastritis	3	
Diverticulum of stomach		1
of duodenum	1	
Benign tumour of stomach		1
Carcinoma of stomach	10 (of 113 cases)	2
Carcinoma of pancreas	1	
No cause demonstrable	4	35

Good pathological records make fascinating reading and every clinician has his day made happier by some laudable correct diagnosis. In almost every instance in the present series where the pathologist demonstrated bedside opinion at fault, the cause of the error could be found in one of those factors well-known in practice which make defeat and not disgrace the outcome of careful clinical effort.

Elaboration of the figures provided in Table I would appear desirable only in respect of those in the necropsy series relating to peptic ulcer. Of the 50 cases of gastric ulcer, 32 were male subjects. In 30

patients the lesion was situated at the middle of the lesser curvature, and in the remainder in the prepyloric region, with the exception of 2 cases who had involvement of the lesser curvature near the cardia. The solitary instance of benign ulcer of the greater curvature occurred in a patient who died of hæmorrhage from one of two ulcers on the lesser curvature. Of the 55 cases of duodenal ulcer, 45 were males and the disease was found on the posterior wall either alone or with associated involvement of the superior or inferior aspects in all except 12 cases in whom there was anterior wall ulceration. More than one bleeding point could be demonstrated with the naked eye in the floor of the ulcer in 17 gastric and 8 duodenal cases. Multiple ulceration of the stomach was found on 5 occasions, of the duodenum in 9 instances and in a further 9 patients in both the stomach and the duodenum.

Although this necropsy series refers only to patients dying of hæmatemesis or melæna, it is of interest for comparison to note that in the autopsy records of perforated peptic ulcer over the same period, this complication affected a greater number of individuals with higher incidence amongst males and more frequent involvement of the duodenum, and caused the greatest mortality in the sixth and seventh decades. Surgery was employed in almost every instance.

THE SOURCE OF THE BLEEDING

Emphasis must be placed at once upon the simple but inescapable fact that all blood lost by hæmatemesis or melæna has a point of origin in relation to the alimentary tract.

Jolted by each new fact or concept in relation to the vascular mechanisms of the gut, the observer experiences a certain relief in the static character of the anatomy of the vessels which are potential sources of hæmorrhage. Above the diaphragm the aorta leaks or bursts into the trachea rather than into the œsophagus. The vena azygos was the site of hæmorrhage in a child included in the clinical series who had swallowed a halfpenny one year previously. Lodged in the long axis of the œsophagus, the coin had not caused complaint until the terminal erosion of this large vein. Well remembered but infrequently encountered, bleeding the result of peptic ulceration or portal hypertension occurs from the intra-mural vessels at the lower end of the œsophagus. Below the diaphragm, aloof and removed from injury, the aorta and inferior vena cava each run their separate course. Equally remote from danger the main stems of the aorta provide the last specifically named branches which by their position and size are the occasional source of fatal exsanguinating hæmorrhage. At point of greatest risk within the wall of the gut, in the substance of the pancreas or in close relationship to these structures run the small vessels, nameless and innumerable, which are the common source of bleeding of any degree of severity. In size capable of admitting the point of a lead pencil and in number usually one and not more than three, the damaged

vessels are commonly as easily discernible as the disease responsible for their rupture. Yet in 4 cases of massive hæmorrhage upon whom autopsy was performed within twenty-four hours of death, causative pathology and bleeding point were alike in their conspicuous absence.

Cause and effect are well seen when bleeding point and focus of pathology occur in association with a gut full of blood. Even in the absence of such bleeding point the disease with good reason may be held responsible for the hæmorrhage. Fourteen cases in the series of peptic ulcer did not exhibit point of bleeding at autopsy. In a recent series of 66 cases of hepatic cirrhosis previously reviewed, 9 of 18 cases dying of hæmatemesis failed to show the customary small laceration overlying the œsophageal varix. Notorious as camouflage, autolytic change and retraction of bleeding point mask the presence of pathology, notably acute ulcer with erosion of arteriole. The very acuteness of the lesion may lead the surgeon astray. In each of 2 cases of my series an acute duodenal ulcer with bleeding point was found at autopsy, having been missed at laparotomy a few hours previously.

The large number of 35 cases in the clinical series in whom the cause of the hæmorrhage was never discovered is in accord with general clinical experience. None of these patients died. None suffered from hæmorrhage of sufficient degree to warrant operation. None was subjected to gastroscopy, a procedure of recognised limitations. Thus two opportunities for obtaining accurate direct information never presented. The third method was never employed. Making comparison with other similar cases in whom diagnosis was established, study of this series suggests that at least 18 of the number suffered from acute ulceration in the gastro-duodenal area. Chronic peptic ulcer was responsible for the remainder with the possible exception of a single case in whom a less common cause for hæmatemesis might ultimately be discovered.

FACTORS PRECIPITATING THE HÆMORRHAGE

Out of sight yet strangely responsive to a wide variety of influences, the alimentary tract fails to provide in the healthy subject indication of constant activity. Although assessment of motor and secretory function of the gastro-duodenal area may be made with a degree of accuracy sufficient for clinical purposes, there does not appear to be at present any method readily available to define the varying blood flow and vascular mechanisms in this important region. With superficial and deep network in the mucous membrane linked with a plexus in the submucous and in the muscular coats, an arrangement affording admirable exposure to injury, the blood vessels show constant alteration in calibre under nervous and biochemical influence. Local demands from the gut add to the burdens already laid by the stresses and strains of the general circulation. Brooding over the whole area is the unquiet and troubled brain. Contending with the fretful elements of the mind,

the blood ripples through the vessels with each light breeze or squall or surges against its containing walls with every storm that blows. Assailed by all these forces, the stomach and duodenum exhibit a resilience and resistance to hæmorrhage that is at once truly remarkable and hitherto inadequately explained.

Commonly unheralded, the long arm of Fate stretches out. Events which yesterday passed without incident today cause hæmorrhage of any degree of severity. In the clinical series of cases of peptic ulcer, 30 patients reported a usual exacerbation for unknown reason of dyspepsia a few days before their hæmorrhage. Fifteen cases suffered from psychiatric upset freely admitted. An equal number described in the few days preceding the bleeding a short period of general malaise, sometimes attended by coryzal symptoms. Nine cases had indulged in dietetic indiscretion and 5 in strenuous exercise. Yet a further 3 had the hæmorrhage shortly after rising in the morning. One patient reported the uncomplicated extraction of many carious teeth the day before his hæmatemesis.

Whatever the effect of these naturally occurring events, the gastro-duodenal area resents surgical interference. Five patients after gastro-enterostomy suffered hæmatemesis from one or more peptic ulcers demonstrated at autopsy, when additional perforation was found in 3 of these cases. Three patients after operative repair of perforation had bleeding from an adjacent ulcer. In 3 cases of fatal hæmorrhage after partial gastrectomy, the pathologist demonstrated bleeding from an infected hæmatoma in one individual, from mucosal lacerations along the line of the clamps in another, but in the third, the source of hæmorrhage could not be defined. Even when surgery is conducted away from the alimentary tract bleeding may occur from an area of new ulceration or a previously existing ulcer. One patient died of hæmatemesis following inguinal herniotomy, and in 2 cases subjected to pelvic floor repair, death resulted from hæmorrhage from a gastric ulcer in the one subject and in the other from multiple superficial gastric erosions. The small number of fatal cases viewed against the large number of operations conducted upon healthy and ulcer subjects shows that the risk, although present, is in no way severe.

Previous attack of hæmatemesis has little effect upon mortality or incidence of recurrence. Throughout the series only one case in every 4 gave the story of antecedent bleeding from the stomach or duodenum.

THE RESULT OF THE BLEEDING

Survey of the varied pathology renders obvious the fact that a satisfactory result cannot always be attained. Even in the absence of mortal disease and of exsanguinating hæmorrhage, the loss of blood may ruin the economy of a body already strained by advancing years or progressive disease commonly of cardio-vascular origin.

Without flurry or fuss, 93 patients (67 per cent.) in the clinical series

of proved and probable peptic ulceration made uninterrupted recovery. Except in few instances in this group, the hæmoglobin level, rightly accepted as inaccurate guide, never fell below 50 per cent, a figure in keeping with the clinical assessment of each case. In the remaining 45 patients (33 per cent), the hæmorrhage was severe with hæmoglobin levels ranging between 20 and 40 per cent. Each case was given transfusion of varying amount of blood and 11 were subjected to operation. A total of 13 patients died. Poised on the very confine of Nature and broken by cerebral vascular accident, prostatism or advanced cardio-respiratory disease, 5 old men tumbled into their graves. One younger man after perforation of a duodenal ulcer and 3 subsequent severe hæmorrhages died shortly after admission to hospital. Two men over the age of 70 years succumbed with continued bleeding, the one refusing operation and the other dying during transfusion. Two males in the sixth decade failed to survive persistent bleeding on conservative treatment. Of the 3 fatalities following operation, all were middle-aged and had previously shown poor response to transfusion. Autopsy failed to reveal obvious cause for death.

TABLE II
Mortality—Peptic Ulcer Group

Age Incidence	Autopsy Series	Clinical Series
10 19		(4)
20 29		(11)
30 39	11	(22)
40 49	16	1 (22)
50 59	23	5 (24)
60 69	34	2 (11)
70 and over	25	5 (9)

Figures in brackets indicate total number of patients in each age group

Ever dramatic, massive hæmorrhage becomes sinister in the absence of manifest bleeding. Two patients with peptic ulcer in the autopsy series died within minutes of the onset of their symptoms of acute anæmia without visible hæmatemesis or melæna, yet at necropsy the intestine was loaded with blood. A further short series of patients died within the hour of arrival at hospital, having sustained a severe hæmorrhage a short time before admission. In all these instances, the cause of death must be associated with the sudden loss of much blood. Less obvious is the reason for fatal issue in those patients who bleed continuously or intermittently at slower rate over longer period and in those who fail to survive operation without demonstrable cause. In presence of marked anæmia, related anoxia and varying degree of sustained hypotension, the cells of the body suffer injury proportional to their circulatory requirements. A single factor cannot be incriminated in the human subject whose metabolism exhibits considerable stability

even under adverse circumstances. Whatever conclusions are drawn from the results of experimental work suggesting the liver to be at fault, a small series of my cases of hæmatemesis failed to show disturbance in hepatic function when subjected to liver efficiency tests commonly employed in clinical practice. The effect of hæmatemesis upon patients with chronic liver disease is well known. Barely one-third of the patients dying with this symptom in my series of cases of hepatic cirrhosis succumbed to their first attack, the others surviving for periods often longer than two years, during which time inexorably there occurred further hæmorrhages and progressive injury to the liver parenchyma. Above all, the human subject is not always fashioned in the same mould, and showing varying degrees of pathological change elsewhere, he cannot show a constant response to hæmorrhage. Throughout the clinical series, the fatal cases were not those who sustained the most severe hæmorrhage or maintained for longest time the lowest blood pressure.

OBSERVATIONS UPON MANAGEMENT

Hæmatemesis is merely an incident in the course of some pathological process the recognition of which in the living subject must frequently await the outcome of successful treatment. Although assistance in diagnosis is often obtained from the clinical history, physical signs of causative pathology notably in peptic ulcer are commonly absent. In 18 cases dying of hæmatemesis in my series of hepatic cirrhosis, 9 showed splenomegaly of which number only 2 had palpable enlargement of the liver.

The patient rapidly exsanguinated by continuing massive hæmorrhage is without hope of relief. The case in whom spontaneous arrest of bleeding is soon forthcoming will get better even in the absence of skilled attention. Between these two extremes and outstanding as therapeutic emergencies are the patients with interrupted or continuing hæmorrhage, and those ill cases in whom after loss of much blood there is doubt if the bleeding has ceased. In all such instances transfusion is required not only to replace blood lost but to assist in the arrest of hæmorrhage. Ancillary to this procedure are rest, sedation and a dietary in accord with the suggestions of Nature and thus the wishes of the patient, rather than in line with the dictates of Lénhartz or Meulengracht. As the blood drips into the patient, at slower rate and in less amount in the elderly subject, a respite is gained giving time to reflect upon the employment of surgery or further conservative treatment. The bulk of the patients recover on medical measures alone.

Dismissal of those cases in the autopsy series in whom the uncomplicated pathology alone ensured a short expectation of life, permits of concentration on the patients dying of hæmatemesis the result of peptic ulceration. Surely in the younger age groups some of these

people could have been saved Glaring up from the records are three outstanding faults—inadequate transfusion, procrastination and infirmity of purpose on part of physician and surgeon alike, and ineffective operative method To be too niggardly in the giving of blood is certainly a worse sin than to continue transfusion after there is every indication for operation Very few pints are necessary before the response of the patient permits of decision concerning further management Operation may give the only chance of survival to the subject with continued bleeding and poor response to conservative treatment Remarkably far from the truth is the statement heard after effort at resuscitation that the condition of the patient is too bad to allow of operation. Although some minor operative procedure or even the mere handling of the stomach or duodenum, may be sufficient to arrest hæmorrhage, the surest method would appear to be partial gastrectomy Loss of life in bleeding peptic ulcer can only be excused in the presence of advanced age, of serious disease elsewhere or of continued hæmorrhage without facility for adequate treatment Whatever the many views expressed upon the indications for operation in this disorder, the competent physician must accept in practice the principle that when his clinical judgment informs him his patient is not making the progress he would wish on account of hæmorrhage the time has come to demand surgery

My thanks are due to the Pathologists of the Royal Infirmary, Edinburgh, for access to their case records and to Professor D M Lyon for permission to include in the clinical series cases observed in his charge

HÆMATEMESIS AND MELÆNA

By W A D ADAMSON, M B, F R C S Ed

Assistant Surgeon, Royal Infirmary, Edinburgh Surgeon, The Deaconess
Hospital, Edinburgh

THE role of the surgeon in the treatment of hæmorrhage from a peptic ulcer is essentially a minor one. As Dr Batty has shown only 5 per cent of such cases are likely to die. While the surgeon, by operating on all cases of hæmorrhage, may obtain a mortality rate as low as 5 per cent, I feel that his essential function is to attempt to save, by surgical measures, some of the 5 per cent that would otherwise die. My aim has therefore been to try to select those cases where surgery may be life-saving, and the more careful the selection the greater will be the service rendered and the fewer the operations.

I will speak this evening only of my own personal experience of the emergency treatment of these cases and will not refer to the work of others. Time is short and while no reference will be made to others' work, you may take it that many of my views are founded essentially on the experience of others as expressed in their writing.

THE CHOICE OF CASE FOR SURGICAL INTERVENTION

It is rarely that surgery is required. Those cases of over 40 years of age, which show a tendency to hæmorrhage, when the ulcer is seen by radiology to be a large one, and is a gastric ulcer at that, should be presented for operation as interval cases. They should be selected and treated as "cold cases," with all the advantages that accrue to the surgery of choice.

The choice of the acute emergency will depend essentially on the response of the individual case to medical treatment. I have taken as indications for operation two severe hæmorrhages, endangering the life of the patient, after the commencement of medical treatment. This forms a fairly definite indication in itself. The size of the hæmorrhage must be estimated, and this is sometimes difficult. When hæmatemesis occurs the quantity actually vomited may be measured. Its consistence and appearance will also indicate the amount of blood lost. With melæna the colour of the stools and the number will help, but as a general rule a large melæna likely to endanger the life of the patient means the passage of dark red blood per rectum in an incontinent manner.

The estimation of the Hb is not of any great value in estimating loss of blood, but I have found the fall in the blood pressure a good measure.

Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 2nd May 1951

